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Proposed Re-evaluation Decision PRVD2016-04

Pyridaben

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Overview

What Is the Proposed Re-evaluation Decision?

After a re-evaluation of the insecticide pyridaben, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of products containing pyridaben for sale and use in Canada.

An evaluation of available scientific information found that most uses of pyridaben products do not pose unacceptable risks to human health or the environment when used according to the proposed label directions. The use of pyridaben on grapes is proposed to be cancelled to address potential risks of concern to human health. As a requirement of the continued registration of remaining pyridaben uses, new risk-reduction measures are proposed for the end-use products registered in Canada. Additional data are being requested as a result of the re-evaluation.

This proposal affects the end-use products containing pyridaben registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for pyridaben and presents the reasons for the proposed re-evaluation decision. It also proposes new risk-reduction measures to further protect human health and the environment.

This consultation document is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the assessment of pyridaben.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2012-02, *Re-evaluation Program Cyclical Re-evaluation* presents the details of the cyclical re-evaluation approach.

For more details on the information presented in this overview, please refer to the Science Evaluation section of this consultation document.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

What Is Pyridaben?

Pyridaben is an insecticide and acaricide registered for use on greenhouse and outdoor ornamentals, greenhouse food crops (peppers, cucumbers and tomatoes), orchard crops, raspberries and strawberries to control mites, whiteflies and pear psylla. It is applied by boom, airblast and backpack sprayers and high volume spray equipment (greenhouse crops) by farmers and farm workers.

Health Considerations

Can Approved Uses of Pyridaben Affect Human Health?

Pyridaben is unlikely to affect human health when used according to the proposed label directions, which include additional risk-reduction measures.

Potential exposure to pyridaben may occur through the diet (food and water), when mixing, loading or applying the product or by entering treated areas. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only those uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, pyridaben was moderately to highly acutely toxic by the oral route of exposure. Low acute toxicity was observed by the dermal route and slight acute toxicity was observed by the inhalation route. Pyridaben was minimally irritating to eyes, non-irritating to skin and did not cause an allergic skin reaction.

Registrant-supplied short, and long term (lifetime) animal toxicity tests, as well as numerous peer-reviewed studies from the published scientific literature were assessed for the potential of pyridaben to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment included clinical signs of toxicity and reductions in weight gain and food intake. There was no indication that the young were more sensitive than the adult animal. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose (ARfD) or chronic reference dose (acceptable daily intake; ADI). An ADI is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Dietary exposure from both food and drinking water was estimated for pyridaben and the metabolites containing the pyridazinone ring. The chronic dietary exposure ranges from 10% to 57% of the ADI for different subpopulations, with the highest value for children aged 1 to 2 years old. The acute exposure to pyridaben ranges from 5% to 28% of the ARfD for different subpopulations, with the highest value for children aged 1 to 2 years old. Thus, acute and chronic dietary risks to pyridaben are not of concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the specified maximum residue limits (MRLs). Pesticide MRLs are specified for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods.

Canadian MRLs for pyridaben are currently specified for a wide range of commodities (MRL database: http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php). Residues in all other agricultural commodities, including those approved for treatment in Canada but without a specific MRL, are regulated under the subsection B.15.002(1) of the Food and Drug Regulations, which requires that residues do not exceed 0.1 ppm. Additional details regarding MRLs can be found in Appendix VIII of this consultation document.

Risks in Residential and Other Non-Occupational Environments

Use of pyridaben in residential settings will be prohibited in order to prevent non-occupational and bystander risks.

Residential exposure may occur from the application of commercial class pyridaben products to fruit trees in residential areas. Based on the hazard classification for all end-use products of pyridaben, uses in residential settings are considered inappropriate. Therefore, the proposed label directions will prohibit the use of pyridaben in residential areas.

Occupational Risks

Occupational mixer/loader/applicator risks are not of concern when pyridaben is used according to the proposed label directions.

Occupational risks are not of concern for agricultural scenarios provided the label-specified protective measures are followed. Based on the label precautions and directions for use reviewed for this re-evaluation, risk estimates associated with mixing, loading and applying activities are not of concern. Updated use instructions are proposed to specify spray volume, and to align personal protective equipment (PPE) requirements.

Occupational postapplication risks are not of concern for most uses when pyridaben is used according to the proposed label directions.

Postapplication occupational risk assessments consider exposures to workers entering treated sites in agriculture. Based on the current use pattern for agricultural scenarios reviewed for this re-evaluation, postapplication risks to workers performing activities such as scouting are not of concern. A restricted-entry interval (REI) of 6 days for the hand harvesting, hand pruning, and disbudding of greenhouse cut flowers is proposed. An REI of 6 days may be agronomically feasible during specific crop production periods, such as between crop cycles.

Occupational postapplication risks are of potential concern for use on grapes.

Postapplication risks to workers performing activities in grapes did not meet target margins of exposure (MOEs) and are of potential concern. The determined REIs for grapes range from 30 to 54 days for high contact activities such as hand harvesting, tying, training and girdling. As these REIs are not considered to be agronomically feasible, the use of pyridaben on grapes is proposed to be removed from labels.

Environmental Considerations

What Happens When Pyridaben Is Introduced Into the Environment?

Pyridaben is not expected to pose an unacceptable risk to the environment when used according to the proposed label directions.

When pyridaben is released into the environment it can enter soil and surface water. In soil, pyridaben can persist. As it binds strongly to soil particles, it is not expected to move downward in the soil and reach groundwater. In aquatic environments, pyridaben rapidly moves out of water and into the sediments, where it could persist. Pyridaben is very rarely detected in available Canadian surface and groundwater monitoring data.

Pyridaben has the potential to move into the atmosphere but it has not been detected in air and it is unlikely to persist in air or be transported to remote locations such as the Arctic. Pyridaben is not expected to accumulate in the tissues of water-dwelling organisms such as fish, however more information is needed on accumulation in sediment-dwelling organisms.

Under controlled laboratory conditions, pyridaben can be toxic to some non-target species such as bees and pollinators, beneficial insects, birds, terrestrial mammals, terrestrial plants and aquatic organisms. If pyridaben is used at label rates without any risk reduction measures, it may cause adverse effects in the organisms listed above. Therefore, mitigation measures are required in order to reduce potential exposure of non-target organisms and reduce environmental risks. When pyridaben is used in accordance with the label and the required risk reduction measures are applied, the resulting environmental risk is considered to be acceptable.

Value Considerations

What Is the Value of Pyridaben?

Pyridaben is important in resistance management.

Pyridaben's uniqueness as the only Group 21A insecticide and acaricide makes it a valuable tool in resistance management of mites and whiteflies. Mites are major pests of a variety of crops and whiteflies are a major pest of greenhouse ornamental crops. In greenhouses, the two-spotted spider mite has developed resistance to most registered insecticides and whiteflies have shown an ability to develop resistance to many pesticides.

In Canada, the limited number of acaricides does not allow for sufficient rotation of the active ingredients to reduce the risk of development of resistance.

Pyridaben contributes to pest management and sustainability when used in rotation with other insecticide and acaricide active ingredients on sites where resistance is known or that are at high risk for it to develop. Therefore, it prolongs the effective life of these other insecticides and acaricides which are prone to development of resistance. There is no resistance to pyridaben in Canada that has been documented.

Proposed Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human health and the environment. These directions must be followed by law. As a result of the re-evaluation of pyridaben, the PMRA is proposing the following further risk-reduction measures for product labels:

Human Health

- To protect postapplication workers in vineyards from postapplication exposure, the use on grapes is proposed to be cancelled (removed from labels).
- To protect the public from non-occupational exposure, it is proposed to prohibit the use of pyridaben in residential areas.

- To protect greenhouse postapplication workers from postapplication exposure, an REI of 6 days is proposed for hand harvesting, hand pruning, and disbudding of greenhouse cut flowers.

- To protect mixer/loader/applicators, a minimum spray volume of 1000 L/ha is proposed for greenhouse cucumbers.

Environment

- Precautionary statements to protect non-target terrestrial and aquatic organisms as well as spray buffer zones for non-target terrestrial and aquatic habitats are proposed. The PMRA is in the process of revising its approach to buffer zones for all chemicals, and will consult broadly on the revised approach prior to implementation. The buffer zone requirements proposed in this document are based on the PMRA's current approach. Buffer zones identified in this proposed decision document may be revised based on any new information received and on any future revisions to the PMRA's approach to calculating buffer zones.

- To reduce the potential for runoff of pyridaben to adjacent aquatic habitats, precautionary statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted are proposed.

What Additional Scientific Information is Being Requested?

Additional confirmatory environmental data are required to be submitted as a requirement of continued registration under section 12 of the *Pest Control Products Act*. The technical registrant of pyridaben must provide the following study or an acceptable scientific rationale to the PMRA within the specified time:

- DACO 9.4.9: Bioaccumulation study in sediment-dwelling invertebrates

Next Steps

During the consultation period, registrants and stakeholder organizations may submit further data that could be used to refine risk assessments (toxicology, exposure, environmental or use information), which could result in revised risk-reduction measures. Stakeholders who are planning to provide information of this type are advised to contact the PMRA early in the consultation period, for advice on studies or information that could be submitted to help refine the relevant risk assessments. Before making a final re-evaluation decision on pyridaben, the PMRA will consider any comments received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on pyridaben. The PMRA will then publish a Re-evaluation Decision[2] that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

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2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*

Science Evaluation

1.0 Introduction

Pyridaben is an insecticide and acaricide belonging to the Insecticide Resistance Action Committee (IRAC) Resistance Management Mode of Action Group 21A.

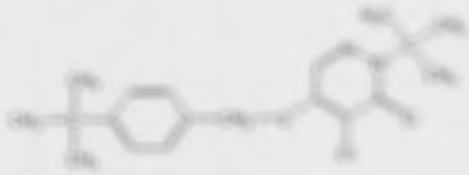
Following the re-evaluation announcement for pyridaben, the registrant of the technical grade active ingredient in Canada indicated continued support for all uses included on the current labels of commercial class end-use products. There are no domestic class end-use products associated with this active ingredient.

The purpose of this re-evaluation is to review existing information on the active ingredient pyridaben, and the currently registered technical and commercial class products containing pyridaben, to ensure that risk assessments meet current standards.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name	Pyridaben
Function	Insecticide and Acaricide
Chemical Family	Pyridazinone
Chemical name	
1 **International Union of Pure and Applied Chemistry (IUPAC)**	2-*tert*-butyl-5-(4-*tert*-butylbenzylthio)-4-chloropyridazin-3(2*H*)-one
2 **Chemical Abstracts Service (CAS)**	4-chloro-2-(1,1-dimethylethyl)-5-[[[4-(1,1-dimethylethyl)phenyl]methyl]thio]-3(2*H*)-pyridazinone
CAS Registry Number	96489-71-3
Molecular Formula	$C_{19}H_{25}ClN_2OS$

Structural Formula	
Molecular Weight	360.9
Purity of the Technical Grade Active Ingredient	95.6
Registration Number	29103

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	< 0.01 mPa
Ultraviolet (UV)/ visible spectrum	Not expected to absorb at λ > 350 nm
Solubility in water at 20°C	0.012 mg/L
n-Octanol/water partition coefficient	$\log K_{ow}$ = 6.37
Dissociation constant	Does not dissociate

2.3 Description of Registered Pyridaben Uses

Appendix I lists all pyridaben products that are registered under the authority of the *Pest Control Products Act*. Appendix II lists all the uses for which pyridaben is currently registered. All uses were supported by the registrant at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments of pyridaben.

Use of pyridaben belongs to the following use-site categories: greenhouse food and non-food crops, terrestrial food and feed crops and outdoor ornamentals.

3.0 Human Health

3.1 Toxicology Summary

Pyridaben is an insecticide/acaricide that belongs to the pyridazinones class of pesticides. It functions by inhibiting mitochondrial electron transport. A detailed review of the toxicological

database for pyridaben was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Most of the studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of toxic effects that may result from exposure to pyridaben.

Following oral administration of single low or high doses of radiolabelled pyridaben, rats showed peak levels in blood within 12 hours and 24 hours, respectively. With repeated low doses, peak concentrations in blood were also within 12 hours. Absorption was incomplete with approximately 80% excreted via feces, half of which was eliminated by bile. Excretion was relatively rapid with most radioactivity excreted by 96 hours regardless of dosing regimen. Negligible amounts were expired in air. No significant differences in excretion patterns were noted as a result of gender, dosing frequency or dose. Pyridaben labeled in the pyridazinone ring was eliminated faster than pyridaben labeled in the benzyl ring, however, more of the benzyl label was recovered in the urine compared to the pyridazinone label. With repeat dosing, pyridaben was broadly distributed to tissues but did not show evidence of bioaccumulation. It was detected in the brain at 2 and 24 hours post-dose but in small amounts (<0.1% of dose).

Metabolism of pyridaben in the rat proceeds with the cleavage of the sulphur bridge followed by oxidation or hydroxylation of the aliphatic side chains on the benzyl or pyridazinone rings; a minor amount of conjugation (primarily glucuronic) also takes place. Numerous metabolites were detected in urine, feces and bile, but with the exception of parent compound, were found at low levels (<6% of administered dose).

In acute oral toxicity studies, pyridaben was highly toxic to the mouse and moderately to highly toxic to the rat. The choice of vehicle influenced toxicity with corn oil enhancing toxicity compared to 1% carboxymethylcellulose. Clinical signs observed in oral studies included decreased motor activity, abnormal posture and gait, piloerection, eye closing and breathing difficulties. Pyridaben was of low toxicity by the dermal route and of slight toxicity by the inhalation route in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits and did not elicit a skin sensitization response in guinea pigs.

No specific target organ was identified with repeated oral dosing. Reduced body-weight gain and food intake were the most commonly affected endpoints. No pronounced sex or species differences were noted in the database although dogs also showed signs of emesis, salivation and gastrointestinal disturbance at low doses. Repeated dermal and inhalation exposures in rats produced a similar toxicological profile as in oral studies (reduced body weight and food intake).

With chronic oral dosing, effects similar to those seen in short-term studies were observed, albeit at slightly lower doses, suggesting a correlation between toxicity and duration of exposure. No evidence of carcinogenicity was seen in dietary studies in the mouse or rat. A battery of genotoxicity tests was negative.

In a dietary two-generation reproductive toxicity test, sensitivity of the young was not apparent. Effects were limited to body weight reductions in parents and pups as well as reduced food intake in parents. Results of oral developmental toxicity studies in the rat and rabbit did not

reveal sensitivity of the young or evidence of malformations. Rat fetuses showed signs of developmental delay at doses affecting body weight and food intake in the dams. In rabbits, an increased incidence of rib variants was noted in fetuses at maternally toxic levels. Two abortions occurred in rabbits at the highest dose level but their relationship to treatment was unclear in the absence of similar effects in the range-finding study at higher dose levels. Oral developmental toxicity studies were conducted by gavage with 1% carboxymethylcellulose as the vehicle, which may be a factor leading to the potential underestimation of toxicity. This concern was lessened as these developmental toxicity studies provided no indication of treatment-related malformations at doses which were toxic to both mother and developing fetus. In a dermal developmental toxicity study, rabbit fetuses exposed to pyridaben had lower body weights than controls at dose levels producing maternal toxicity.

In an acute oral neurotoxicity study in rats, clinical signs of toxicity and reduced reflex response were observed on the day of dosing followed by weight loss. Although the study was conducted with 1% carboxymethylcellulose as the vehicle, it was noted that clinical signs were seen at a similar dose of pyridaben as in the acute lethality study employing corn oil as a vehicle. Effects in the 13-week dietary neurotoxicity study in rats were limited to reduced body-weight gain and food consumption. No evidence of sensitivity was observed in a dietary developmental neurotoxicity study in rats. Maternal effects consisted of reductions in body weight, weight gain, food intake and activity levels. At a higher dose, slight increases in clinical signs and a marginal shift in gestation length were noted in dams. Offspring at the lowest effect level demonstrated reduced body weight at post-natal day 21, likely the result of consumption of treated diet rather than gestational or lactational exposure to pyridaben. At a higher dose, offspring showed slight increases in activity post-weaning, and in adult male pups, an equivocal effect on learning and memory. There were no neuropathological findings in any of the neurotoxicity studies.

A mammalian metabolite and environmental degradation product identified as PB-7 was less toxic than pyridaben in an acute oral lethality study in rats. PB-7 was also negative for genotoxicity in a bacterial reverse mutation assay.

Most of the published literature on pyridaben has focused on its inhibitory activity of NADH-ubiquinone reductase, the energy-conserving complex that is commonly known as Complex I. The inhibition of glutamate-dependent mitochondrial respiration in rat liver was demonstrated with pyridaben as early as 1994 (see References section, PMRA #2356211); this inhibition was found to be specific to NADH CoQ_1 (otherwise known as NADH-ubiquinone reductase) in bovine heart. Pyridaben inhibited bovine Complex I with greater potency than rotenone, a well-known Complex I inhibitor (PMRA #2356207). A similar pattern of inhibition in respiratory chain enzymatic activity (NADH-cytochrome reductase activity) was observed in rat brain mitochondria incubated with pyridaben or rotenone (PMRA #2342424).

Given that brain tissues from humans with Parkinson's Disease (PD) exhibit reduced Complex I activity, pyridaben has been the subject of research in the scientific literature investigating risk factors for the development of PD or other parkinsonian disorders. Parkinsonism is a spectrum disorder that refers to a variety of different pathologies that can cause Parkinson's-like symptoms (movement disorders). Risk factors for parkinsonism are varied and include genetics, injury or chemical exposure to name a few. Parkinson's Disease makes up approximately 80% of cases of

parkinsonism. It is generally characterized by the loss of nigrostriatal dopaminergic neurons in the substantia nigra pars compacta (SNpc) in the brain, the appearance of intracellular eosinophilic inclusions called Lewy bodies and the depletion of striatal dopamine (PMRA #2356222). These Lewy bodies contain proteins including α-synuclein and ubiquitin. Lewy bodies are not considered a requirement for PD diagnosis, however, as some PD cases have reportedly lacked this feature (PMRA #2356214). Clinical features such as bradykinesia, rigidity, postural instability and resting tremor are apparent when dopamine depletion reaches 80% and when 40-60% of SNpc dopaminergic neurons are lost.

As pyridaben and rotenone are both Complex I inhibitors, comparisons can be drawn. Rotenone is often used in a neurotoxicant-induced animal model for parkinsonism, replicating many of the features of PD. Repeated intravenous or subcutaneous infusion with rotenone resulted in degeneration of a subset of nigrostriatal dopaminergic neurons, the formation of cytoplasmic inclusions and the development of parkinsonian behavioral features such as rigidity and tremors in Lewis rats (PMRA #2356204, 2356216). Some researchers have questioned the specificity of the neurodegenerative findings with rotenone as well as the relevancy of the tested route (PMRA #2356214, 2356206, 2356210, 2356219). More recently, mice exposed orally to rotenone were found to exhibit significant neuronal degeneration in the substantia nigra, behavioral impairment (reduction in endurance time on rota-rod treadmill) and increased α-synuclein immunoreactivity in surviving neurons in a time-dependent manner; these effects were observed at a dose causing mortality in the first week of study only and no effect on body weight (PMRA #2356213).

Despite having a similar mode of action (inhibition of Complex I), rotenone and pyridaben are structurally dissimilar. Like rotenone (PMRA #2361180), pyridaben is poorly absorbed from the gastrointestinal tract following oral exposure and typically affects body-weight gain in laboratory animals upon repeated exposure. Toxicokinetic data with pyridaben suggest that this lipophilic compound can cross the blood-brain barrier. Rotenone's lipophilic properties also allow it to easily cross the blood-brain barrier (PMRA #2356205). In human neuroblastoma cells (PMRA # 2356217), pyridaben was more potent than rotenone in inducing cell death, causing ATP depletion and inhibiting State 3 respiration in mitochondria isolated from rat brains. Greater oxidative damage was observed with pyridaben in neuroblastoma cells compared to the same dose of rotenone. Pyridaben was found to be similar in potency to rotenone at displacing ^{3}H-dihydrorotenone (DHR) binding to Complex I in isolated rat brain mitochondria. The reason for the lack of correlation between the displacement of DHR binding with cell death and ATP depletion was unknown although the study authors postulated that it may involve differences in binding to Complex I or the metabolism of pyridaben to highly reactive sulfoxide and sulfone derivatives. In the in vitro neuroblastoma system, both α-tocopherol and coenzyme Q_{10} were protective against pyridaben and rotenone toxicity.

Although pyridaben was not tested in dopaminergic neurons in the aforementioned studies, mid-brain slice cultures from post-natal day 10 Lewis rats exposed to pyridaben for one week showed marked dose-related pruning and loss of dendritic and axonal projections.

To further explore the potential link to PD, pyridaben was added to neurons co-cultured with astrocytes from mouse brains that were engineered to suppress or overexpress DJ-1 protein levels. DJ-1 protein serves to protect cells against oxidative stress and cell death; it regulates

expression of mitochondrial uncoupling proteins in dopaminergic neurons of the SNpc as well as regulates astrocyte inflammatory response among other functions. Genetic DJ-1 deficiency has been linked to familial PD and, sporadic PD reactive astrocytes have been shown to over express DJ-1. Results indicated the DJ-1 deficient astrocytes were less neuroprotective for neuronal survival than wild-type astrocytes when exposed to pyridaben, duplicating earlier work performed by the same author with rotenone. Substances that inhibited Complex II, III or IV did not demonstrate this difference, pointing to a selective impairment in neuroprotection with Complex I inhibitors. DJ-1 over-expressing astrocytes were also compared with wild-type astrocytes against pyridaben with the former demonstrating augmentation of neuroprotection (PMRA #2356215).

Young male mice exposed to 3.5 mg pyridaben/kg bw/day for 7 days via subcutaneous pump demonstrated significant neurodegeneration in the substantia nigra as well as a significant increase in α-synuclein aggregates. Following transcriptome sequencing of mRNA from the ventral mid-brain and striatum and pathway analysis, the authors reported that there was a concordance of signalling pathways of pyridaben with two other neurotoxicants (paraquat and maneb) with relevance to PD pathogenesis (PMRA #2356208).

Findings in the animal studies that would support the hypothesis that pyridaben is linked to PD (or parkinsonism) are: loss of neurons in the substantia nigra (in vivo, subcutaneously), increase in α-synuclein aggregates (in vivo, subcutaneously) and decreased mitochondrial Complex I activity (in vitro). In contrast, there is a lack of information for pyridaben on dopamine depletion in the striatum, the relative selectivity for nigrostriatal dopamine compared to other brain regions, clinical observations of bradykinesia, resting tremors or rigidity and the alleviation of these behavioural effects by dopamine agonists. The positive findings with pyridaben occurred via routes of limited relevance to the current risk assessment; however, it is noteworthy that rotenone administration has produced positive results in animal studies using the same routes of dosing (subcutaneous and intravenous) as well as with oral dosing. Although relevant clinical signs were noted with high dose levels of pyridaben in the acute oral toxicity studies in rats and mice (abnormal gait and decreased motor activity) and acute neurotoxicity study in rats (tremors and slow or poorly coordinated righting reflex), these signs were noted in the presence of other clinical signs and could reflect general systemic toxicity. No similar observations were noted in repeat-dose studies. No evidence of neuropathology was recorded in Sprague-Dawley rats in an acute (gavage) neurotoxicity study or in dietary subchronic or developmental neurotoxicity studies although examination was limited to hematoxylin and eosin staining, a relatively insensitive method for assessing neurons and glial cells. Furthermore, the lack of neuropathology findings is tempered by the knowledge that species, strain, gender and age can yield variable results in chemical-induced parkinsonian models (for example, mouse can be more sensitive than rat; Lewis rats can be more sensitive than Sprague-Dawley rats).

Although a number of epidemiological studies have suggested an association between pesticide and/or insecticide use and PD, no studies could be located in the open literature that have demonstrated an association between pyridaben use and PD. Too few cases of pyridaben use among the participants in the Farming and Movement study, a case control study of PD nested in the Agricultural Health Study, precluded an assessment for this chemical (PMRA #2356218).

This study did, however, demonstrate a positive association between rotenone and PD (odds ratio = 2.5; 95% confidence interval, 1.3 – 4.7).

In conclusion, there is some uncertainty on pyridaben's role within the context of the development of PD or parkinsonism. In vitro mechanistic data and animal data support an association between pyridaben exposure (albeit by a route of limited relevance) and mitochondrial dysfunction and nigrostriatal degeneration. Comparative in vitro data with rotenone (a substance with a similar mode of action) suggest that pyridaben is of equal and could even have greater potency. Despite the uncertainty regarding pyridaben's role within the context of neurodegenerative disease, given that rotenone has demonstrated an effect on nigrostriatal dopaminergic neurons with oral dosing, an additional database uncertainty factor of threefold was applied in the risk assessment to account for the lack of data addressing the potential for specific neuronal damage via the routes of expected exposure. Through the application of this additional factor, the risk assessment is considered sufficiently protective of these concerns. In the event that the registrant proposes to address this uncertainty (for example, through a new study), they are strongly encouraged to obtain input from the PMRA prior to generating such data.

Results of the toxicology studies conducted on laboratory animals with pyridaben are summarized in Table 1, Appendix IV. The toxicology endpoints for use in the human health risk assessment are summarized in Table 2, Appendix IV.

3.1.1 *Pest Control Products Act* Hazard Considerations

For assessing risks from potential residues in food or from products used in and around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for pyridaben. The database contains a full complement of required studies including developmental toxicity studies in rats and rabbits (the latter by the oral and dermal route of exposure) and a reproductive toxicity study in rats. In addition, a developmental neurotoxicity study was submitted.

No sensitivity of the young was noted in any of the available studies; all effects in the fetus and young animal were noted at dose levels that produced maternal toxicity, typically in the form of reduced body weight and food intake. Effects in the fetus included delayed development in the rat and rib variations (oral study) or reduced body weight (dermal study) in the rabbit. Although the choice of vehicle in the developmental toxicity studies may have led to an underestimate of toxicity, the studies provided no indication of treatment-related malformations at doses which were toxic to both the mother and developing fetus. Offspring in the reproductive toxicity and developmental neurotoxicity study demonstrated reduced body weight. At a higher dose in the developmental neurotoxicity study, offspring showed slight increases in activity post-weaning and in adult male pups, an equivocal effect on learning and memory.

Overall the database is adequate for determining the sensitivity of the young. There is low concern for sensitivity of the young and effects on the young are well-characterized. While an effect on learning and memory is considered a serious endpoint, the concern was tempered by the equivocal response, the presence of concomitant maternal toxicity, and the ample margin to endpoints selected for risk assessment. On the basis of this information, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Cancer Risk Assessment

There was no evidence of carcinogenicity and therefore, a cancer risk assessment was not required.

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to pyridaben from potentially treated imported foods is also included in the assessment. These dietary assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high. The PMRA Science Policy Notice SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessments procedures.

Residue estimates used in the dietary risk assessment may be conservatively (using upper bound estimates) based on the maximum residue limits (MRLs). They may also be based on the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's (CFIA) National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program (USDA PDP). Specific and default processing factors as well as specific information regarding the percentage of crop treated may also be incorporated to the greatest extent possible.

In situations where the need to mitigate dietary exposure has been identified (the risk exceeds 100% of the reference dose), the following options are considered. Dietary exposure from Canadian agricultural uses can be mitigated through changes in the use pattern. Revisions of the use pattern may include such actions as reducing the application rate or the number of seasonal applications, establishing longer pre-harvest intervals (PHIs), and/or removing uses from the label. In order to quantify the impact of such measures, new residue chemistry studies which reflect the revised use pattern are required. These data would also be required in order to amend MRLs to the appropriate level. Imported commodities which have been treated also contribute to the dietary exposure, and are routinely considered in the risk assessment. The mitigation of

dietary exposure that may arise from treated imports is generally achieved through the amendment or specification of MRLs.

Acute and chronic dietary risk assessments for pyridaben were conducted using the Dietary Exposure Evaluation Model – Food Commodity Intake Database (DEEM–FCID™, Version 2.14), which incorporates consumption data from the United States Department of Agriculture Pesticide Data Program Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.3.1 Determination of Acute Reference Dose (ARfD)

To estimate acute dietary risk for the general population, the acute neurotoxicity study in the rat with a no-observed-adverse-effect level (NOAEL) of 44 mg/kg bw was selected for risk assessment. At the lowest-observed-adverse-effect level (LOAEL) of 80 mg/kg bw, clinical signs and weak reflex responses were observed. These effects were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to onefold. The composite assessment factor (CAF) is therefore 100. Although there is some uncertainty concerning pyridaben's potential for specific neuronal damage, given the progressive nature of the neurodegeneration in question, it is unlikely that a single exposure to pyridaben by the oral route would be sufficient to elicit a response of concern. Accordingly, a database uncertainty factor was not added to the acute reference dose as it was considered overly conservative for this scenario.

The ARfD was calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{44 \text{ mg/kg bw}}{100} = 0.4 \text{ mg/kg bw of pyridaben}$$

3.3.2 Acute Dietary Exposure and Risk Assessment

Acute dietary risk was calculated considering the highest ingestion of pyridaben that would be likely on any one day, and using food consumption and food residue values. The expected intake of residues is compared to the ARfD, which is the dose to which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, then acute dietary exposure is not of concern.

The acute dietary (food + water) exposure assessment was based on upperbound estimates using MRLs and American tolerances for residue estimates. Where no MRLs or tolerances were available, the general MRL of 0.1 ppm was used. No refinements were applied.

The acute dietary exposure estimate of pyridaben from food and water for the general population is 8% (95th percentile) of the ARfD. Exposure estimates for all population subgroups range from 5% to 28% of the ARfD, and therefore are not of concern. The acute dietary exposure and risk assessment estimates are presented in Appendix V.

3.3.3 Determination of Acceptable Daily Intake (ADI)

To estimate risk of repeated dietary exposure for the general population, the one-year dog study with a NOAEL of 0.5 mg/kg bw/day was selected. At the LOAEL of 1 mg/kg bw/day (from a second one-year dog study) clinical signs and reduced body weight and body-weight gain were observed. The one-year dog studies provide the lowest NOAEL in the database; however, the long-term mouse and rat studies are considered co-critical with NOAELs of 0.81 and 1.1 mg/kg bw/day respectively. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. A database uncertainty factor of threefold was added to account for the lack of data to address the potential for specific neuronal damage via a relevant route of exposure. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor has been reduced to onefold. The CAF is therefore 300.

The ADI was calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.5 \text{ mg/kg bw/day}}{300} = 0.002 \text{ mg/kg bw/day of pyridaben}$$

The ADI provides a margin of >2000 to the NOAEL for the equivocal effect on learning and memory in the rat developmental neurotoxicity study and is thus considered protective for the young.

3.3.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues was then compared to the ADI. When the expected intake of residues is less than the ADI, then chronic dietary risk is not of concern.

The dietary risk assessment for pyridaben considered exposure from all food and water sources that could potentially contain pyridaben. Residue estimates for animal commodities were based on anticipated residues calculated for feed residue data, while residue estimates for most plant commodities were mainly based on CFIA pesticide residue monitoring data. Where Cfia Monitoring Data Was Not Available, United States Department Of Agriculture Pesticide Data Program Monitoring Data, Field Trial Data, Mrls Or American Tolerances Were Used. Experimental processing factors and food supply information were also used in the assessment where applicable. Refinement for percent crop treated (%CT) and domestic production data versus import data were also used. As such, the chronic dietary exposure assessment is considered to be refined (not worst-case estimates of exposure).

The chronic dietary exposure estimate of pyridaben from food and water for the general population is 19% of the ADI, and therefore is not of concern. Exposure estimates for all population subgroups range from 10% to 57% of the ADI, and are also not of concern. The chronic dietary exposure and risk assessment estimates are presented in Appendix V.

3.4 Exposure from Drinking Water

3.4.1 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of pyridaben in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. An overview of how the EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of pyridaben in groundwater were calculated using the PRZM-GW model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZM-GW are based on the movement of pesticide into shallow groundwater with time. EECs of pyridaben in surface water were calculated using the PRZM/EXAMS model, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a small reservoir.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate. Table 1, Appendix X lists the application information and main environmental fate characteristics used in the simulations. A number of initial application dates between March 1 and June 15 were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Table 2, Appendix X.

3.4.2 Water Monitoring Data

In addition to water modelling, a search for water monitoring data on pyridaben in Canada and the the United States was undertaken. Pyridaben was very rarely detected in both countries. For details, please see Appendix XI.

3.4.3 Drinking Water Exposure and Risk Assessment

Drinking water exposure was considered in both the acute and chronic dietary exposure assessments with the EEC point estimates incorporated directly in the dietary (food + drinking water) assessments. Please refer to Sections 3.3.2 and 3.3.4 for details. The comparison between the exposure assessment performed on food + water residues versus food only residues showed a minor exposure increase of less than 1% of the reference doses when water was included in the acute or the chronic dietary assessments.

3.5 Occupational and Non-Occupational Risk Assessment

The occupational and non-occupational risks are estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not

necessarily mean that exposure will result in adverse effects. However, MOEs less than the target MOE require measures to mitigate (reduce) risk.

3.5.1 Toxicological Endpoints for Occupational and Residential Risk Assessment

For the dermal risk assessment, the NOAEL of 100 mg/kg bw/day from the three-week dermal toxicity study in rats was selected as the point of departure. At the LOAEL of 300 mg/kg bw/day, reductions in body weight and body weight gain were observed. This study was considered appropriate for risk assessment as it used a relevant route and assessed parameters sensitive to pyridaben exposure such as body weight. Although a slightly lower NOAEL for body weight change was observed in maternal animals in the dermal rabbit developmental toxicity study, the NOAEL from the three-week dermal toxicity study was selected as it was the highest NOAEL below the lowest LOAEL for body weight change in a repeat-dose dermal study. The target MOE for the short-, intermediate-, and long-term scenario is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and threefold for the lack of data to address the potential for specific neuronal damage via a relevant route of exposure. For the long-term scenario, the additional threefold uncertainty factor was considered sufficient to also account for the uncertainty associated with the selection of a short-term study for the long-term risk assessment given that the durational effects noted with pyridaben were only slight. For residential risk assessment, the *Pest Control Products Act* factor has been reduced to 1-fold for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section.

For the inhalation risk assessment, the no-observed-adverse-effect concentration (NOAEC) of 0.003 mg/L (= NOAEL of 0.78 mg/kg bw/day) from the four-week inhalation toxicity study in rats was selected as the point of departure. At the lowest-observed-adverse-effect concentration (LOAEC) of 0.01 mg/L (2.6 mg/kg bw/day), reductions in body weight, bodyweight gain and food intake were observed. This study was considered appropriate for risk assessment as it used a relevant route and assessed parameters sensitive to pyridaben exposure such as body weight. The target MOE for the short-, intermediate- and long-term scenario is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and threefold for the lack of data to address the potential for specific neuronal damage via a relevant route of exposure. For the long-term scenario, the additional threefold uncertainty factor was considered sufficient to also account for the uncertainty associated with the selection of a short-term study for the long-term risk assessment given that the durational effects noted with pyridaben were only slight. For the residential risk assessment, the *Pest Control Products Act* factor has been reduced to onefold for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section.

3.5.1.1 Dermal Absorption

No dermal absorption factor was required for the pyridaben risk assessments since the dermal endpoint is based on a dermal toxicity study.

3.5.2 Occupational Exposure and Risk Assessment

Workers can be exposed to pyridaben through mixing, loading or applying the pesticide, or when entering a treated site to conduct activities such as scouting and/or handling of treated crops.

3.5.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

There are potential exposures to mixers, loaders, and applicators. The following scenarios were assessed:

- Mixing/loading of wettable powders (in water soluble packaging)
- Groundboom application to strawberries and raspberries (postharvest)
- Manually-pressurized hand held spray wand applications to greenhouse vegetables, greenhouse ornamentals and outdoor ornamentals
- Mechanically-pressurized hand held spray gun applications to greenhouse vegetables, greenhouse ornamentals and outdoor ornamentals
- Backpack applications to greenhouse vegetables, greenhouse ornamentals and outdoor ornamentals
- Mistblower (automated) applications to greenhouse vegetables and greenhouse ornamentals
- Airblast application to apples, pears, peaches, nectarines, cherries (sweet and tart) and grapes

In the absence of data, there is no means to assess the exposure incurred during applications made by hand held mistblower. Consequently, a statement prohibiting this application equipment will be added to end-use product labels.

For the purposes of the risk assessment, greenhouse ornamentals have been subdivided into "greenhouse potted ornamentals" and "greenhouse cut flowers". The term "greenhouse cut flowers" includes all ornamentals cut by hand.

Based on the number and timing of agricultural applications per year, exposure is considered to be of short- to intermediate-term (up to several months) in duration. Handler exposure was estimated based on the levels of personal protection described on the product labels:

A. **Mixing, Loading and Applying (All equipment):**
Open mixing and loading. Open cab application.
Personal Protective Equipment for all tasks: A single layer, chemical resistant gloves, respirator.

B. **Mixing, Loading and Applying (Greenhouse equipment only):**
Open mixing and loading.
personal protective equipment for all tasks: Chemical resistant coveralls over a single layer, chemical resistant gloves, respirator.

Dermal and inhalation exposures were estimated using data from the Pesticide Handlers

Exposure Database (PHED), Version 1.1. The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment.

One chemical specific exposure study was submitted by the registrant in support of the re-registration of pyridaben. A number of limitations limit confidence in the results of this greenhouse mixer/loader/applicator study, and no statistically robust characterization of exposure could be derived for use in the risk assessment for pyridaben.

In addition, since target MOE's were achieved using standard assumptions and exposure values from PHED, refinement of the mixer, loader and applicator assessment beyond the PHED based estimates was not required.

In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing chemical-resistant coveralls or a respirator. This was estimated by incorporating a 90% clothing protection factor for chemical resistant coveralls and 90% protection factor for a respirator into the unit exposure data.

Inhalation exposures were based on light inhalation rates (17 LPM), except for backpack applicator scenarios, which were based on moderate inhalation rates (27 LPM).

The results of the mixer, loader, and applicator risk assessment are presented in Tables 1 and 2 of Appendix IX. The occupational risk estimates associated with mixing, loading and applying pyridaben are not of concern.

3.5.2.2 Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers entering treated sites to conduct agronomic activities involving foliar contact (such as scouting). Based on the pyridaben use pattern, outdoor postapplication exposure is considered to be short-term (< 30 days) in duration. In greenhouse settings, there is potential for overlapping crop cycles and pest pressures. As such, postapplication exposure in greenhouses is considered to be long-term in duration. However, in the case of pyridaben, the occupational endpoints and target MOE's for the dermal and inhalation routes are not substantially affected by duration (Table 2, Appendix I).

Potential exposure of postapplication workers was estimated using activity-specific transfer coefficients (TC's) and dislodgeable foliar residue (DFR) values. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in the field. TC's are specific to a given crop and activity combination (for example, hand harvesting apples, scouting and hand weeding) and reflect standard clothing worn by adult workers.

Activity-specific TC's from the Agricultural Re-entry Task Force were used to estimate postapplication exposure resulting from contact with treated foliage at various times after application.

Three chemical-specific DFR studies were considered in the re-evaluation of pyridaben in order to determine foliar residues and dissipation rates. These studies were performed on almonds, citrus, greenhouse roses and chrysanthemums. The studies were conducted using the number of applications and application intervals that are consistent with the registered use pattern. Based on a comparison of application equipment, foliage types, application rates, crop canopies and study conditions, DFR data from the greenhouse (roses and chrysanthemums) and almond studies were used to estimate foliar residues on greenhouse ornamental and outdoor crops, respectively.

Due to the uncertainties associated with extrapolating DFR data from a greenhouse ornamentals study to a risk assessment for greenhouse vegetables, the study's DFR data was not applied in the postapplication risk assessment of greenhouse vegetables treated with pyridaben. Instead, the standard assumptions of 25% of the application rate as the initial DFR and 0% as the daily dissipation rate were applied.

For workers entering a treated site, restricted-entry Intervals (REIs) are calculated to determine the minimum length of time required before people can safely enter after application. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE.

The outdoor occupational postapplication exposure and risk assessments are summarized in Table 5, Appendix IX. No changes to the current label REIs, for the outdoor uses are proposed, with the exception of grapes.

The determined REIs for grapes range from 30 to 54 days for high contact activities, such as hand harvesting, tying, training and girdling. As these REIs are not considered to be agronomically feasible, the use of pyridaben on grapes is proposed to be removed from labels.

The greenhouse occupational postapplication exposure and risk assessments are summarized in Table 6, Appendix IX. For greenhouse vegetables and potted ornamentals, postapplication risks were acceptable for all activities at the label REI of 12 hours. For greenhouse cut flowers, REIs range from 12 hours to 6 days. An REI of 6 days may be agronomically feasible during specific crop production periods, such as between crop cycles.

Further refinements to the current risk assessment may be possible through the submission of detailed use information, postapplication exposure data or dislodgeable foliar residue data.

5.5.2 Non-Occupational and Residential Exposure and Risk Assessment

No residential applicator risk assessment was required for pyridaben, as there are no registered residential products. Pyridaben is registered for use on outdoor ornamentals, however, the use is restricted to nursery stock. Residential postapplication exposure may occur from the application of commercial class pyridaben products to fruit trees in residential areas. Based on the hazard

classification for all end-use products of pyridaben ("PYRIDABEN 15EC"), use in residential settings is considered inappropriate. Therefore, the proposed conditions of use will preclude the use of pyridaben in residential areas.

5.6 Aggregate Exposure and Risk Assessment

An aggregate assessment combining dietary (food + water) exposure with residential exposure was not conducted as there are no residential uses registered for pyridaben.

5.7 Cumulative Risk Assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. For the current re-evaluation, the PMRA did not identify information indicating that pyridaben shares a common mechanism of toxicity with other pest control products. Therefore, there is no requirement for a cumulative assessment at this time.

6.0 Impact on the Environment

6.1 Fate and Behaviour in the Environment

Data on the fate and behaviour of pyridaben and its major transformation products are summarized in Table 3, Appendix X.

Pyridaben enters the environment when used as an insecticide for control of insect pests on a variety of crops. When applied, pyridaben can be carried away from the area of application by spray drift and runoff; therefore, it could reach and contaminate nearby surface water bodies. Pyridaben is practically insoluble in water, has high volatility and is predicted to volatilize from moist soil and water. However, pyridaben has a high tendency to sorb to soil, so volatilization from soils will likely be limited. Due to pyridaben's low solubility and high level of sorption, it is unlikely to leach into groundwater and will remain bound to soil during runoff events. The Groundwater Ubiquity Score and comparison to the leaching criteria of Cohen et al. also indicates that pyridaben is unlikely to leach.

In water, pyridaben transforms quickly, with photoransformation being the major route of dissipation and biotransformation contributing to a lesser extent. Hydrolysis is not an important route of transformation of pyridaben.

In aerobic water/sediment systems, pyridaben is non-persistent in water and moderately persistent to persistent in aerobic sediment. In soil, aerobic and anaerobic biotransformation routes are not expected to be major transformation processes. In aerobic soil, pyridaben is moderately persistent to persistent and in anaerobic soil is classified as persistent. Although data are limited, it appears that the dissipation times in soils are longer at cooler temperatures as compared to warmer temperatures, which is of importance due to potential for applications during colder seasons (October) in Canada.

Pyridaben was non-persistent to moderately persistent in Canadian terrestrial field studies and non-persistent in northern American terrestrial field studies. In outdoor aquatic microcosm studies conducted in Florida and Alabama, pyridaben was shown to be non-persistent in water and non-persistent to slightly persistent in sediment.

Major transformation products include PB-22, PB-14, P-14, PB-7, W-1 and B-3. Only B-3 exhibited maximum concentrations at study termination in aqueous phototransformation studies. The transformation products P-14, PB-7 and PB-22 were either not detected or did not leach below 15cm in US field studies.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications (Tables 4, 5 and 6 of Appendix X). Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (protection at the community, population, or individual level) (Table 7, Appendix X).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1, except for beneficial insects which have an LOC = 2, and bees which have an LOC = 0.4). If the screening level risk quotient is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

Risk of pyridaben to terrestrial organisms (Table 8, Appendix X) was based upon evaluation of toxicity data for the following (Table 7, Appendix X):

- Acute and chronic studies with mammal and bird species representing vertebrates
- Acute and chronic studies on earthworms
- Acute oral and contact studies using the technical grade active ingredient and end-use product with bees
- Acute contact studies with beneficial arthropods
- Toxicity studies on terrestrial non-target plant species

Terrestrial Invertebrates

Earthworms

Pyridaben is not toxic to earthworms and is not expected to pose a risk.

Bees

Honeybees are potentially at risk from a single application of pyridaben at the maximum registered single application rate on both a contact and oral exposure basis. Bee brood studies indicate that larval honeybees are at potentially risk to all registered application rates. Mitigative label statements are proposed to minimize exposure of pyridaben to pollinators.

Predators and parasites: Beneficial insects

Beneficial arthropods are potentially at risk from all registered application rates of pyridaben. Even after 14 days, residues of pyridaben still caused >50% mortality at half of the maximum registered application rates. Pyridaben has the potential to adversely affect beneficial insects; therefore, mitigative label statements are proposed to minimize exposure of pyridaben to beneficial insects.

Terrestrial Vertebrates

Birds

The risk assessment for birds indicates the use of pyridaben poses a negligible risk to birds at the maximum registered cumulative application rate on an acute basis. There is the potential for reproductive risk for all size classes of birds both on-field and off-field due to drift (Table 9, Appendix X). In cases where potential risk exists, birds would have to consume a significant amount of contaminated food (35-71% of their daily diet) before the level of concern is exceeded. Label statements are proposed to warn users of these potential risks.

Mammals

There is negligible risk to terrestrial mammals on an acute basis both on-field and off-field due to drift. The risk assessment indicates that there is a potential reproductive risk to terrestrial mammals both on-field and off-field due to drift (Tables 10 and 11, Appendix X).

A refined risk assessment (Table 12, Appendix X) shows that the risk is decreased significantly using mean nomogram residue values in food, however, it is not entirely mitigated. In cases where potential risk exists, mammals would have to consume between 26-83% of their daily diet as contaminated food before the level of concern is reached. Label statements are proposed to warn users of these potential risks.

Terrestrial Plants

Non-Target Vascular Plants

There is a potential risk to non-target terrestrial plants at the maximum registered cumulative application rate, but not at the single maximum application rate. Label statements are proposed to warn users of these potential risks. Spray buffer zones are proposed to mitigate the risks to non-target terrestrial plants that may result from the application of pyridaben (Table 2, Appendix XII).

4.2.2 Risks to Aquatic Organisms

Risk of pyridaben to freshwater aquatic organisms was based upon evaluation of toxicity data for the following (Table 7, Appendix X):

- Acute and chronic invertebrate studies
- Acute and chronic freshwater fish studies
- Acute algae studies
- Acute vascular plant (duckweed)

Risk of pyridaben to marine organisms was based upon evaluation of toxicity data for the following (Table 7, Appendix X):

- Acute and chronic invertebrate studies
- Acute fish studies
- Acute marine diatom studies

The assessment of the risk of bioaccumulation of pyridaben is based on the evaluation of bioaccumulation tests on freshwater fish. Risk to amphibians was based on the endpoints from acute and chronic freshwater fish studies.

Aquatic organisms can be exposed to pyridaben from spray drift or run off. At the screening level, EECs are calculated based on a direct application to water at the maximum cumulative rate, which is taking into account the maximum labelled application rate, the application interval and

the dissipation of the compound in aquatic systems. Bodies of water of two depths are considered for the risk assessment. A depth of 15 cm is representative of a seasonal water body used by amphibians during the reproduction period. A depth of 80 cm is representative of a permanent water body for all other aquatic organisms. The screening level EECs are based on the maximum seasonal application rate of 540 g a.i./ha applied two times with a 30-day interval. The EECs were determined to be 107 µg a.i./L in 80 cm water and 568 µg a.i./L in 15 cm water. These EECs are above the maximum theoretical solubility limit of pyridaben in pure water (12-22 µg a.i./L) so the screening level risk is overestimated, however, this is further refined below taking into consideration more realistic environmental concentrations.

Refined aquatic risk assessments were conducted for a spray drift scenario (59% off field deposition rate based on air blast application with fine droplet size) and a run off scenario. The EECs for drift were 63 µg a.i./L (80 cm water depth) and 335 µg a.i./L (15 cm water depth). The EECs used for acute runoff risk determination were the daily peak concentrations for both the 80 and 15 cm water bodies obtained via ecoscenario modeling. The EEC used for the chronic run off risk assessment was the 21-day mean concentration for both the 80 and 15 cm water bodies.

A final refinement of the risk assessment was conducted using the 96-hour and 21-day runoff EECs from the ecoscenario water modeling for each particular region of Canada that was modelled. This offers a more realistic run-off exposure scenario and is comparable to the 48- and 96-h acute toxicity tests conducted with various aquatic biota and the longer term chronic tests. The RQs were calculated using the specific 96-h EEC for acute risk and the specific 21-day EEC for chronic risk for each Canadian region that was modeled using different scenarios for berry and tree uses.

Screening Level Risk Assessment

Screening level RQs for all aquatic biota were above the LOC (Table 13, Appendix X) when applied at the maximum application rate using air-blast equipment indicating that all aquatic biota are at risk.

Refined Risk Assessment

The LOC was exceeded for most aquatic biota, including freshwater and marine invertebrates, freshwater and marine fish and amphibians, on both an acute and chronic basis (where data was available). The LOC was not exceeded for freshwater algae and freshwater vascular plants for runoff scenarios, however, the LOC was exceeded for spray drift. The LOC was also exceeded for marine invertebrates on an acute and chronic basis for both spray drift and runoff. The LOC was exceeded for marine fish on an acute basis from spray drift, and runoff. The LOC was not exceeded on an acute basis for marine algae due to run off, however, it was exceeded due to spray drift (Table 14, Appendix X).

Further Refinement of Risk Assessment

Although further refinement of the risk assessment using runoff EECs for each region does reduce the risk associated with pyridaben use at the maximum application rates currently

registered in Canada, the LOC was exceeded for freshwater and marine invertebrates, amphibians and freshwater fish in most regions. A risk was observed for marine fish only in the Atlantic region for berry uses. A risk was not found for freshwater algae and vascular plants and marine diatoms in any Canadian region that was modelled (Table 15, Appendix X).

There is a potential risk to non-target aquatic biota at the registered application rates, therefore, label statements are proposed to warn users of these potential risks. In addition, spray buffer zones from 5 to 120 metres are proposed to mitigate the risks to aquatic organisms that may result from the application of pyridaben (Table 2, Appendix XII).

Bioaccumulation of Pyridaben in Biota

Although the log K_{ow} of pyridaben (6.37) indicates that bioaccumulation may be a concern in fish, empirical evidence (bioconcentration factors of 139-2360, not detectable in fish after 7 days of depuration, large number of transformation products in fish) indicates that this is not the case for pelagic-dwelling biota. However, given that pyridaben will preferentially sorb to sediment, confirmatory data on bioaccumulation in sediment-dwelling invertebrates are required.

5.0 Value

Pyridaben is an insecticide and acaricide that belongs to the Resistance Management Mode of Action Group 21A. Pyridaben is the only Group 21A insecticide and acaricide registered in Canada, which makes it a valuable tool in resistance management of mites and whiteflies. Pyridaben contributes to pest management and sustainability by playing an important role in resistance management, when used in rotation with other insecticide and acaricide active ingredients on sites where resistance is known or that are at high risk for it to develop. Therefore, it prolongs the effective life of these other insecticides and acaricides that are prone to development of resistance. There is no resistance to pyridaben in Canada that has been documented.

In greenhouses, the two-spotted spider mite has developed resistance to most other registered acaricides. Whiteflies have shown an ability to develop resistance to many pesticides, and are a major pest of ornamental greenhouse crops. There are one to four crop cycles per year and multiple numbers of insecticide applications needed per crop cycle. However, there are few products to control mites and whiteflies registered for greenhouse ornamentals, especially for cut flowers.

Acaricide resistance is a serious concern of orchardists and berry producers, and a limited number of acaricides are registered for strawberries and grapes.

Appendix III lists all registered alternative active ingredients to pyridaben for those site/pest combinations of commercial class products for which potential risks of concern have been identified.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, pyridaben and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[3] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Pyridaben does not meet Track 1 criteria, and is not considered a Track 1 substance. Refer to Table 16 of Appendix X for comparison with Track 1 criteria.
- Pyridaben does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[4]. The list is used as described in the PMRA Notice of Intent NOI2005-01[5] and is based on existing policies and regulations including DIR99-03 and DIR2006-02[6], as well as taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade pyridaben and the current end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

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3 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

4 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613, *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

5 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

6 DIR2006-02, PMRA Formulants Policy and Implementation Guidance Document.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA that include adverse effects to health and the environment. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. Incidents were searched and reviewed for the active ingredient pyridaben.

As of November 2014, the PMRA had received one incident report related to human health for the active ingredient pyridaben. One human and two domestic animals were affected in the incident. There was insufficient information provided on pesticide exposure to make the determination if the reported effects in the human and the domestic animals were associated with the active ingredient pyridaben. The incident report was considered in this evaluation and did not affect the risk assessment.

A search of available databases (PMRA incident reporting, USEPA Environmental Incident Information System database v. 2) did not yield any environmentally related incident reports.

8.0 Organisation for Economic Co-operation and Development Status of Pyridaben

Canada is a member of the Organisation for Economic Co-operation and Development (OECD), which groups 34 member countries and provides governments with a setting in which to discuss, develop and perfect economic and social policies.

As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of an active ingredient in other jurisdictions, including OECD member countries. In particular, decisions by an OECD member to prohibit all uses of an active ingredient for health or environmental reasons are considered for relevance to the Canadian situation.

As of 2 May 2014, pyridaben is acceptable for use in other OECD countries, including the United States, Australian and European Union member states. No decision by an OECD member country to prohibit all uses of pyridaben for health or environmental reasons has been identified.

9.0 Proposed Re-evaluation Decision

The PMRA is proposing that most uses of pyridaben are acceptable for continued registration with implementation of proposed risk-reduction measures.

The proposed mitigation measures are listed in Appendix XII.

9.1 Proposed Regulatory Actions

9.1.1 Proposed Regulatory Action Related to Human Health

- The use of pyridaben on grapes is proposed to be cancelled (removed from labels) due to potential postapplication risks of concern to workers, based on currently available information.

- Based on the hazard classification for all end-use products of pyridaben, uses in residential settings will be prohibited in order to prevent nonoccupational and bystander risks.

- Based on the exposure assessments, label amendments proposed to mitigate exposure include harmonizing personal protective equipment on all product labels, a minimum spray volume of 1000 L/ha on greenhouse cucumbers and an increased REI of 6 days for hand harvesting, hand pruning, and disbudding of greenhouse cut flowers. The health risk-reduction measures proposed are consistent with current labelling requirements.

9.1.2 Proposed Regulatory Action Related to the Environment

- In order to mitigate the potential effects of pyridaben to non-target organisms in terrestrial and aquatic habitats, precautionary statements, use restrictions and spray buffer zones (Table 2, Appendix XII) are proposed. Information that could facilitate buffer zone refinement may be submitted during the consultation period. The PMRA is in the process of revising its approach to buffer zones for all chemicals and will consult broadly on the revised approach prior to implementation. The buffer zone requirements proposed in this document are based on the PMRA's current approach. Buffer zones identified in this proposed decision document may be revised based on any new information received and on any future revisions to the PMRA's approach to calculating buffer zones.

9.2 Additional Data Requirements

9.2.1 Data Requirements Related to the Environment

Additional confirmatory environmental data are required to be submitted as a requirement of continued registration under section 12 of the *Pest Control Products Act*. The technical registrant of pyridaben must provide the following study or an acceptable scientific rationale to the PMRA:

- DACO 9.4.8: Bioaccumulation Study in Sediment-dwelling Invertebrates
  Study requested by the USEPA, using Guideline Number 850.1710 - Bioconcentration in oysters.

9.3 Next Steps

During the consultation period, registrants and stakeholder organizations may submit further data that could be used to refine risk assessments (toxicology, exposure, environmental or use information), which could result in revised risk-reduction measures. Stakeholders who are planning to provide information of this type are advised to contact the PMRA early in the consultation period for advice on studies or information that could be submitted to help refine the relevant risk assessments. Before making a final re-evaluation decision on pyridaben, the PMRA will consider all comments received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on pyridaben. The PMRA will then publish a Re-evaluation Decision that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

10.0 Supporting Documentation

PMRA documents, such as Regulatory Directive DIR2012-02, *Re-evaluation Program Cyclical Re-evaluation*, and DACO tables can be found on the Pesticides and Pest Management portion of Health Canada's website. PMRA documents are also available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3798; e-mail: pmra.infoserv@hc-sc.gc.ca

The federal TSMP is available through Environment Canada's website.

List of Abbreviations

µg	microgram
ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	body-weight gain
Bz	benzyl ring label
CAF	composite assessment factor
CAS	chemical abstracts service
CFIA	Canadian Food Inspection Agency
cm	centimetres
cm^2/h	centimetres squared per hour
CMC	carboxymethylcellulose
D	day
DACO	data code
DER	data evaluation record
DFR	dislodgeable foliar residue
DHR	1'H-dihydrorotenone
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
EAF	exposure adjustment factor
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
EFSA	European Food Safety Authority
et al.	and others
EUP	end-use products
F_1	first filial generation
F_2	second filial generation
FIR	food ingestion rate
FOB	functional observational battery
g	gram
GAP	Good Agricultural Practice
GD	gestation day
ha	hectare(s)
HAFT	highest average field trial
IRAC	Insecticide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_f	Freundlich adsorption coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	*litre*
LC_{50}	*lethal concentration 50%*
LD_{50}	*lethal dose 50%*
LOAEL	*lowest-observed-adverse-effect level*
LOC	*level of concern*
LOEC	*lowest-observed-effect concentration*
LOQ	*limit of quantitation*
LPM	*litres per minute*
LR_{50}	*lethal rate 50%*
mg	*milligram*
mL	*millilitre*
MOE	*margin of exposure*
mPa	*millipascal*
MP HG	*mechanically pressurized hand-held sprayer*
MP HW	*manually pressurized hand-held sprayer*
MRL	*maximum residue limit*
MTDB	*maximum theoretical dietary burden*
N/A	*not applicable*
NOAEL	*no-observed-adverse-effect level*
NOAEC	*no-observed-adverse-effect concentration*
NOEC	*no-observed-effect concentration*
NOEL	*no-observed-effect level*
OECD	*Organisation for Economic Co-operation and Development*
P	*parental generation*
PCP	*pest control product*
PCPA	*Pest Control Products Act*
PD	*Parkinson's disease*
PHED	*Pesticide Handlers Exposure Database*
PHI	*pre-harvest interval*
PMRA	*Pest Management Regulatory Agency*
PND	*postnatal day*
PPE	*personal protective equipment*
ppm	*parts per million*
PVA	*polyvinyl alcohol*
Py	*pyridaxinone ring label*
REI	*restricted-entry interval*
RLD	*repeat low dose*
RQ	*risk quotient*
SHD	*single high dose*
SLD	*single low dose*
SNpc	*substantia nigra pars compacta*
TC	*transfer coefficient*
TGAI	*technical grade active ingredient*
TRR	*total radioactive residue*
TSMP	*Toxic Substances Management Policy*
URMULE	*User Requested Minor Use Label Expansion*
USC	*use site category*

USDA	United States Department of Agriculture
USDA PDP	United States Department of Agriculture Pesticide Data Program
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WSP	wettable powder in water soluble packaging
/	and/or
()	formulae
↑	increased
↓	decreased
%CT	percent crop treated

Appendix I Pyridaben Products Registered in Canada as of June 25, 2012

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (% a.i.)
25133	Technical	Gowan Company, L.L.C.	Pyridaben Technical Miticide/Insecticide	N/A	99.4
25134	Commercial	Gowan Company, L.L.C.	Sanmite Miticide/Insecticide	Wettable powder	75
25135	Commercial	Gowan Company, L.L.C.	Nexter Miticide/Insecticide	Wettable powder	75
25229	Commercial	Plant Products Co. Ltd.	Dyno-mite Miticide/ Insectide Wettable Powder Formulation	Wettable powder	75

This table excludes discontinued products or products with a submission for discontinuation.

Appendix II Pyridaben Uses Registered in Canada as of June 25, 2012

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Use Supported by the Technical Registrant	Comments
				Maximum Single (g a.i./ha)	Maximum Cumulative (g a.i./ha/year)				
USE-CATEGORY 5: Greenhouse Food Crops									
Cucumbers	Two-spotted spider mite	Wettable powder	Foliar; high volume spray equipment	525[1]	4200[1]	2 applications per crop cycle; 2-4 crop cycles per year[1]	28	Yes	The end-use product labels have application rates expressed per 1000 L or per hectare. The technical registrant clarified that they support the product rate of 280 g or 10 (28 g) PVA bags in 1000 L of water. They recommended spray volumes for cucumber, pepper and tomato, which are 500 to 2500 L, 500 to 2000 L and 300 to 1500 L, respectively, of spray solution per broadcast hectare. As a result of comments from growers regarding the number of applications per crop cycle and number of crop cycles per year, the registrant agreed to support the recommended number of applications and number of crop cycles per year (see footnotes for each crop), which was used to calculate the maximum cumulative application rate per year used in the risk assessment.
Peppers				420[2]	840[2]	2 applications per crop cycle; 1 crop cycle per year[2]	30[b]		
Tomatoes (non-processing)				315[3]	630[3]	2 applications per crop cycle; 1 crop cycle per year[3]	30[b]		
USE-CATEGORY 6: Greenhouse Non-Food Crops									
Ornamentals	Two-spotted spider mite	Wettable powder	Foliar; high volume spray equipment	420[4]	3360[4]	2 applications per crop cycle; 1-4 crop cycles per year[4]	28[b]	Yes	The end-use product labels have application rates expressed per 1000 L or per hectare. The technical registrant clarified that the supported product rate for two-spotted spider mites is 140-280 g/1000 L or 5-10 (28 g) PVA bags in 1000 L of water. For whiteflies, 280-420 g/1000 L or 10-15 (28 g) PVA bags in 1000 L of water. They recommended 440 to 2000 L of spray solution per broadcast hectare. As a result of comments from growers regarding the number of applications per crop cycle and number of crop cycles per year, the registrant agreed to support 2 applications per crop cycle and a maximum of 4 crop cycles per year, which was used to calculate the maximum cumulative application rate used in the risk assessment (see footnotes 4 and 5).
	Whiteflies (sweet potato, greenhouse)			630[5]	5040[5]	2 applications per crop cycle; 1-4 crop cycles per year[5]			

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Use Supported by the Technical Registrant	Comments
				Maximum Single (g a.i./ha)	Maximum Cumulative (g a.i./ha/year)				
USC 13 and 14: Terrestrial Feed and Terrestrial Food Crops									
Apples	European Red Mite, Apple Rust Mite	Wettable powder	Foliar; air-blast, upright boom, backpack	225	900 on the same orchard	2	30[b]	Yes	
	Two-spotted Spider Mite, McDaniel Spider Mite			225 or 450					
USE-CATEGORY 14: Terrestrial Food Crops									
Cherries (sweet and tart)	European Red Mite	Wettable powder	Foliar: air-blast, upright boom, backpack	225	450 on the same orchard	1	N/A	Yes	
	Two-spotted Spider Mite, McDaniel Spider Mite			225 or 450					
Grapes	European Red Mite	Wettable powder	Foliar: air-blast, upright boom, backpack	225	450	1	N/A	Yes	
	Two-spotted Spider Mite McDaniel Spider Mite			225 or 450					
Peaches Nectarines (Ontario only)	European Red Mite	Wettable powder	Foliar: air-blast, upright boom, backpack	225	450 on the same orchard	1	N/A	Yes	
	Two-spotted Spider Mite, McDaniel Spider Mite			225 or 450					
Pears	European Red Mite,Pear Rust Mite	Wettable powder	Foliar: air-blast, upright boom, backpack	225	1080 on the same orchard	2	30	Yes	

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Use Supported by the Technical Registrant	Comments
				Maximum Single (g a.i./ha)	Maximum Cumulative (g a.i./ha/year)				
	Two-spotted Spider Mite, McDaniel Spider Mite			225 or 450					
	Pear Psylla			450-540					
Raspberries (Post-harvest application only)	European Red Mite	Wettable powder	Foliar: air-blast, over the row boom sprayer, backpack	225	900	2	30[b]	Yes	
	Two-spotted Spider Mite McDaniel Spider Mite			225 or 450					
Strawberries	European Red Mite	Wettable powder	Foliar: boom sprayer	225	900	2	15[b]	Yes	
	Two-spotted Spider Mite McDaniel Spider Mite			225 or 450					
USC 27: Ornamentals Outdoor									
Outdoor ornamentals	European Red Mite, Two-spotted Spider Mite	Wettable powder	Ground equipment	420[c]	840[c]	2	28[b]	Yes	The end-use product labels have application rates expressed per 1000 L or per hectare. The technical registrant clarified that the supported product rate is 280 g or 10 (28 g) PVA bags in 1000 L of water. They recommended a spray volume of 500 to 2000 litres of spray solution per broadcast hectare which was used to calculate the active ingredient application rate per hectare (see footnote 6).

[1] Greenhouse cucumbers: Product rate supported by the registrant is 280 g or 10 bags (28 g) PVA bags in 1000 L of water. Recommended spray volume is 500 to 2500 L of spray solution per broadcast hectare. Calculated active ingredient rate range is 105-525 g a.i./ha (spray volume 500 to 2500 L of spray solution per broadcast hectare). Active ingredient rate range (maximum of 2 applications per crop cycle) is 105-1050 g a.i./ha/crop cycle. Maximum cumulative application rate (4 crop cycles/year) is 4200 g a.i./ha/year.

[2] Greenhouse peppers: Product rate supported by the registrant is 280 g or 10 bags (28 g) PVA bags in 1000 L of water. Recommended spray volume is 500 to 2000 L of spray solution per broadcast hectare. Calculated active ingredient rate is 105-420 g a.i./ha (spray volume 500-2000 L/ha). Active ingredient rate range (maximum of 2 applications per crop cycle is 105-840 g a.i./ha/crop cycle). Maximum cumulative application rate (1 crop cycle/year) is 840 g a.i./ha/year.

[3] Greenhouse tomatoes: Product rate supported by the registrant is 280 or 10 (28 g) PVA bags in 1000 L of water. Recommended spray volume is 300 to 1500 L of spray solution per broadcast hectare. Calculated active ingredient rate range is 63-315 g a.i./ha (spray volume 300 to 1500 L/ha). Active ingredient rate range (maximum of 2 applications per crop cycle) is 63-630 g a.i./ha. Maximum cumulative application rate is 630 g a.i./ha (maximum of 1 crop cycle per year).

[4] Greenhouse ornamentals: Product rate supported by the registrant for two-spotted spider mite is 140 -280 g/1000 L or 5-10 (28 g) PVA bags in 1000 L of water. Recommended spray volume is 480 to

2000 L of spray solution per broadcast hectare. Calculated active ingredient rate is 46.2-420 g a.i. /ha (spray volume 440 to 2000 L/ha). Active ingredient rate range (maximum of 2 applications per crop cycle) is 46.2-840 g a.i. /ha/crop cycle. Maximum cumulative active ingredient rate is 3360 g a.i. /ha/year (maximum of 4 crop cycles per year).

[7] Greenhouse ornamentals: Product rate supported by the registrant for whiteflies is 280-420g/ 1000 L or 10-15 (28 g) PVA bags in 1000 L of water. Recommended spray volume is 440 to 2000 L of spray solution per broadcast hectare. Calculated active ingredient rate for whiteflies is 92.4-630 g a.i. /ha (spray volume 440 to 2000 L/ha). Active ingredient rate range (maximum of 2 applications per crop cycle) is 92.4-1260 g a.i. /ha . Maximum cumulative active ingredient rate is 5040 g a.i. /ha/year (maximum of 4 crop cycles per year).

[8] Outdoor ornamentals: Product rate supported by the registrant is 280 g or 10 (28 g) PVA bags in 1000 L of water. Recommended spray volume is 500 to 2000 L of spray solution per broadcast hectare. Calculated active ingredient rate is 105-420 g a.i. /ha (spray volume 500 to 2000 L/ha). Active ingredient rate range (maximum of 2 applications per year) is 105-840 g a.i. /ha. Maximum cumulative active ingredient rate is 840 g a.i. /ha/year.

Appendix III Alternative Registered Active Ingredients to Pyridaben for Site-Pest Combinations for which Risks of Concern Have Been Identified as of 12 April 2014

Site(s)	Pest(s)	Alternative Registered Active Ingredients (Resistance Management Group No.)[1]	Suggested Use of pyridaben?	If concern, Food Risk (comments)?	Identification of Risk Assessment Concerns
Grapes	European red mite Two-spotted spider mite McDaniel spider mite	Group 10: mitochon Group 21: pyrimidifen UN: bifenazate Other: mineral oil, potassium salts of fatty acids	Yes	Yes	No re-registration rate re-evaluation. Re-proposed MOE range from 30 to 90 days for high contact activities. These MOE are not considered to be agronomically feasible. Re-use of pyridaben on grapes is proposed to be removed from labels.
Strawberries	European red mite Two-spotted spider mite McDaniel spider mite	Group 10: clofentezine, etoxazole Group 21: pyrimidifen, tebufenpyrad Group 25: cyenopyrafen (two-spotted spider mite) Other: potassium salts of fatty acids	Yes	Yes	A buffer zone of 120 metres is proposed to ameliorate risks for the protection of freshwater habitats with a mean depth < 1m.
Greenhouse ornamentals (cut flowers)	Two-spotted spider mite	Group 10: acephate (registered for a limited number of ornamentals), etoxazole, clofentezine Group 21: pyrimidifen Group 25: cyenopyrafen UN: bifenazate Other: potassium salts of fatty acids	Yes	Yes	No re-registration rate re-evaluation. Re-proposed MOE range from 15 hours to 6 days. (30 MOE of 5 days may be agronomically feasible, timing specific crop production periods only).
	Whiteflies (sweet potato, greenhouse)	Group 10: acephate (registered for a limited number of ornamentals), pymetrozine, clofentezine, etoxazole, sulfoxaflor Group 4: acetamiprid, imidacloprid, thiamethoxam Group 7: cyantraniliprole, pymetrozine Group 9B: pymetrozine Group 21: pyrimidifen Other: potassium salts of fatty acids	Yes	Yes	

[1] This is a list of registered options only. Health Canada does not endorse any of the options listed. A number of the listed alternative active ingredients are in the process of being re-evaluated by Health Canada, including: fenpyroximate, clofentezine, etoxazole, tebufenpyrad, and thiamethoxam. The registration status of active ingredients under re-evaluation may change pending the final regulatory decision.

[2] IRAC Mode of Action Classification scheme Version 7.3 (February 2014) http://www.irac-online.org/documents/moa-classification/?ext=pdf
UN – uncoupler of oxidative phosphorylation via disruption of the proton gradient; 3 – sodium channel activators; 4 – nicotinic acetylcholine receptor (nAChR) agonists; 5 – nicotinic acetylcholine receptor agonists/antagonists; 6 – chloride channel activators; 7 – juvenile hormone mimics; 9B – selective homopteran feeding blockers; 10 – mite growth inhibitors, affect CHS1; 21 – mitochondrial electron transport inhibitor (METI) acaricides and insecticides; 25 – mitochondrial electron transport inhibitor (METI) II and III compounds; 28 – ryanodine receptor modulators; 29 – chordotonal organ TRPV channel modulators; 32 – inhibitors of acetyl CoA carboxylase; Other: non-specific (multi-site) inhibitors, unknown or uncertain MoA; NC – not classified; "Co-formulated" indicates that the two active ingredients are present in the same product.

Appendix IV Toxicology Endpoints for Health Risk Assessments

Table 1 Summary of Toxicology Studies for Pyridaben

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in absolute weight and relative (to body weight) weight unless otherwise noted.

Study Type / Animal / PMRA #	Study Results
Toxicokinetic Studies	
Absorption, distribution, excretion and metabolism – oral (gavage) Sprague Dawley rat PMRA #1172616, 1172679 ^{14}C-labelled in pyridazinone (Pz) or benzyl (Bz) ring	Single low dose (SLD) or repeat low dose (RLD) of 3 mg/kg bw or single high dose (SHD) of 30 mg/kg bw (values expressed as % of administered dose) Absorption: Peak concentration in blood at 0.25 – 12 hours (SLD, RLD) or 24 hours (SHD) Distribution: At 24 hours, mostly found in gastrointestinal tract (SLD, SHD). At 168 hours, RLD animals showed low levels in gastrointestinal tract, fat and blood with Pz label and gastrointestinal tract, small and large intestine, liver, eye, lymph node, Harderian gland, fat and skin with Bz label. Total radioactivity remaining at 168 hours (RLD) was <0.05% (Pz label) or 0.2-0.3% (Bz label). Detected in brain at 2 and 24 hours (both labels) but in small amounts (< 0.1 % of dose) Excretion: High levels (75-97%) excreted in faeces with all regimes. In urine, 3-7% excreted with Pz label and 10-24% excreted with Bz label. Negligible amounts detected in expired air. Most excreted within 96 hours (SLD, SHD) or 72 hours (RLD) Metabolism: In urine, 7-13 metabolites detected with Pz label, each < 2.9%. With Bz label, 13-22 urinary metabolites were detected, each < 5.3%. In faeces, metabolites numbered 11-14 (Pz label) or 14-21 (Bz label). Parent compound accounted for 20-41% regardless of dosing regime. Metabolism involves the cleavage of the sulphur bridge followed by oxidation or hydroxylation of the aliphatic side chains on the benzyl or pyridazinone rings.
Distribution, excretion and metabolism – oral (gavage) Sprague Dawley rat (bile cannulated) PMRA #1172680 ^{14}C-labelled in pyridazinone (Pz) or benzyl (Bz) ring	Single high dose (SHD) of 30 mg/kg bw (values expressed as % of administered dose) Excretion and tissue levels at 24 hours were as follows: Faeces: 26-30% (Pz), 18-51% (Bz) Bile: 26-28% (Pz), 22-30% (Bz) Urine: 1-2% (Pz), 2-4% (Bz) GI tract: 32-36% (Pz), 21-39% (Bz) Liver: 0.7% (Pz), 2-4% (Bz) Plasma: not detected Approximately 30 metabolites were detected in each of urine, faeces or bile samples. With the exception of parent compound (10-25%), no other metabolite was seen in the faeces at significant levels (in other words, >2%). Principal metabolites in the urine included P9, a mercapturic acid conjugate (1-2% with Pz label) and B11 and B15 (6% with Bz label). Metabolism includes a minor amount of conjugation, primarily from glucuronic acid.
Absorption, distribution and excretion – dermal	Single low dose (SLD) of 3 mg/kg bw Absorption: Peak blood levels occurred at 96 hours.

Study Type / Animal / PMRA #	Study Results
Sprague Dawley rat PMRA #1172686 ^{14}C-labelled in pyridazinone (Pz) or benzyl (Bz) ring	Distribution: At 168 hours, highest levels detected in fat, kidney and liver followed by low levels in blood, ovary, uterus, heart and lung. Excretion: Mostly eliminated in the faeces. Urinary elimination of the absorbed fraction was greater for the Bz label than the Pz-label.
Acute Toxicity Studies	
Acute oral toxicity Sprague Dawley rat PMRA #1145963	LD_{50} = 1100 mg/kg bw (♂); 570 mg/kg bw (♀) (1% CMC) Signs of toxicity included ↓motor activity, abnormal posture, abnormal faeces, piloerection, stained fur, eye closing, abnormal gait and bradypnea **Moderate acute toxicity**
Acute oral toxicity Sprague Dawley rat PMRA #2294504	LD_{50} = 1350 mg/kg bw (♂); 820 mg/kg bw (♀)(1% CMC) Signs of toxicity included ↓motor activity, ataxia, hunched posture, ungroomed appearance, lethargy, breathing irregularities, prone posture **Moderate acute toxicity**
Acute oral toxicity Sprague Dawley rat PMRA #2294503	LD_{50} = 161 mg/kg bw (♂); 181 mg/kg bw (♀) (maize oil) Signs of toxicity included ungroomed appearance, underactivity, staggering gait, hairloss, piloerection, salivation, hunched posture, lethargy, prone position, bradypnea, tachypnea, hyperpnea, cold to touch **High acute toxicity**
Acute oral toxicity CD-1 mouse PMRA #1145964	LD_{50} = 424 mg/kg bw (♂); 383 mg/kg bw (♀)(1% CMC) Signs of toxicity included ↓motor activity, abnormal posture, piloerection, eye closing, abnormal gait, bradypnea, cyanosis, stained fur and mucous faeces **High acute toxicity**
Acute oral toxicity CD-1 mouse PMRA # 2294505, 2294507	LD_{50} = 253 mg/kg bw (♂); 205 mg/kg bw (♀)(1% CMC) Signs of toxicity included ↓motor activity, prone or crouching posture, ataxia, urinary incontinence, piloerection, cool to touch, disappearance of righting reflex, bradypnea, ptosis, diarrhea. Necropsy findings on gastrointestinal tract. **High acute toxicity**
Acute dermal toxicity Sprague Dawley rat PMRA #1145950	LD_{50} > 2000 mg/kg bw No mortality or clinical signs observed **Low acute toxicity**
Acute dermal toxicity NZW rabbit PMRA #2294509	LD_{50} > 2000 mg/kg bw No mortality observed. Clinical signs limited to transient breathing irregularities **Low acute toxicity**
Acute inhalation (whole body) toxicity	4hr LC_{50} = 0.66 mg/L (♂); 0.62 mg/L (♀) (white carbon 100:8 w/w)

Study Type / Animal / PMRA #	Study Results
F344 rat PMRA #1145968	Signs of toxicity included eye closing, abnormal respiration, lacrimation, stained fur **Slight acute toxicity**
Eye irritation NZW rabbit PMRA #1145948	Well-defined /slight conjunctivitis, slight chemosis and ocular discharge at one hour post-dosing. No lesions present at 72 hours. **Minimally irritating.**
Dermal irritation NZW rabbit PMRA #1145951	**Non-irritating**
Dermal sensitization (Maximisation assay) Hartley guinea pig PMRA #1145953	**Non-sensitizing**
Short-Term Toxicity Studies	
13-week oral toxicity (diet) CD-1 mouse PMRA #1146317, 1157241	NOAEL = 4.1 mg/kg bw/day (♂); 14.7 mg/kg bw/day (♀) ≥ 13.0/14.7 mg/kg bw/day:↓bwg; ↓bw (♂); ↓water intake (♀) ≥ 40.1/43.1 mg/kg bw/day: ↑urea; ↓water intake (♂); ↓bw, ↓food intake (♀) 119/125 mg/kg bw/day: ↓food intake, ↑alkaline phosphatase, ↑aspartate aminotransferase (♂); ↑ornithine carbamyltransferase
13-week oral toxicity (diet) CD rat PMRA #1145960	NOAEL = 4.9 mg/kg bw/day (♂); 2.6 mg/kg bw/day (♀) ≥ 5.5 mg/kg bw/day: ↓bw , ↓bwg (♀) ≥ 11.6/12.8 mg/kg bw/day: ↓food intake, ↓total protein; ↓bw, ↓bwg (♂); ↓albumin (♀) 25.7/27.7 mg/kg bw/day: ↑urea, gamma-glutamyl transpeptidase, alkaline phosphatase Animals left to recover for 4 weeks still showed effects on bw and in females, urea, protein and albumin levels
4-week oral toxicity (capsule) Beagle dog PMRA #1146286	Supplementary (range-finding) ≥ 10 mg/kg bw/day: emesis, soft stool/diarrhea 100 mg/kg bw/day: salivation (1 ♀) 300 mg/kg bw/day: weight loss (1), ↓food intake, salivation (♂)
4-week oral toxicity (diet) Beagle dog PMRA #1145956	Supplementary (range-finding) All treated dogs (2.3 – 12.3 mg/kg bw/day) showed loss of appetite, weight loss, thin appearance , cold to touch, ↓food intake. Some showed weakness, depletion of body fat, pale kidneys and small testes
13-week oral toxicity (capsule) Beagle dog	NOAEL not established, LOAEL = 2.4 mg/kg bw/day ≥ 2.4 mg/kg bw/day: frothy emesis, ↓food intake, depletion of body fat; diarrhea,

Study Type / Animal / PMRA #	Study Results
PMRA # 1145974	soft stool, salivation (♂); inappetance, thin, ↓bw, ↓bwg (♀) ≥ 12 mg/kg bw/day: ↓bw, ↓bwg (♂) 60 mg/kg bw/day: mortality (1♂) 300 mg/kg bw/day: mortality (all survivors sacrificed at week 10), prostration, diarrhea, vomiting, inappetance, thinness, dehydration ↓activity, dry nose, salivation, weakness, ↓weight loss
13-week oral toxicity (capsule) Beagle dog PMRA #1145961, 1145973	NOAEL = 1 mg/kg bw/day ≥ 4 mg/kg bw/day: salivation; trembling, ↓bwg (♂); food-like emesis (♀) 16 mg/kg bw/day: emesis, soft stool/diarrhea; salivation, ↓bwg (♀)
52-week oral toxicity (capsule) Beagle dog PMRA #1145975	NOAEL not established, LOAEL = 1 mg/kg bw/day ≥ 1 mg/kg bw/day: ↓bw, ↓bwg; salivation (♂) ≥ 4 mg/kg bw/day: emesis; salivation (♀) ≥ 16 mg/kg bw/day: diarrhea (♂) 32 mg/kg bw/day: emaciation (1), diarrhea, hepatocellular hypertrophy (1), hypocellularity of bone marrow (1), skeletal muscle atrophy (1) (♀)
52-week oral toxicity (capsule) Beagle dog PMRA #1145976	NOAEL = 0.5 mg/kg bw/day 0.5 mg/kg bw/day: salivation (for 1-4 weeks), soft stool (for 1-6 weeks), diarrhea (for 1-2 weeks), emesis (for 1-4 weeks); ↓bw, ↓bwg (♀)
3-week dermal toxicity Sprague Dawley rat PMRA #1145955	NOAEL = 100 mg/kg bw/day (systemic toxicity) ≥ 100 mg/kg bw/day: squamous cell hyperplasia of skin ≥ 300 mg/kg bw/day: ↓bwg; ↓alanine aminotransferase (♂); ↓bw (♀) 1000 mg/kg bw/day: ↓food intake in 1st week; ↓bw (♂); ↓albumin (♀)
4-week inhalation toxicity Sprague Dawley rat PMRA #1145957	NOAEL = 0.003 mg/L (0.78 mg/kg bw/day) ≥ 0.003 mg/L: intermittent dried red nasal discharge, ↓alanine aminotransferase; ↓albumin (♀) 0.01 mg/L: anogenital staining, ↓bw, ↓bwg, ↓food intake in 1st week Effects reversible upon 2-week cessation of dosing
Chronic Toxicity/Oncogenicity Studies	
78-week oncogenicity (diet) CD-1 mouse PMRA #1145993, 1145994, 1157236	NOAEL = 0.81 mg/kg bw/day (♂); 2.8 mg/kg bw/day (♀) ≥ 2.8 mg/kg bw/day: ↓bw, ↓bwg (♂) 8.9/9.7 mg/kg bw/day: slight ↓food intake; slight ↑mortality, ↓food efficiency, ↑amyloidosis (♂); ↓bw, ↓bwg (♀)

Study Type / Animal / PMRA #	Study Results
	No evidence of carcinogenicity
104-week chronic toxicity and oncogenicity (diet) CD rat PMRA #1145989, 1145990, 1145991, 1145992, 1157234, 1157235	NOAEL = 1.1/1.5 mg/kg bw/day (♂/♀) ≥ 3.2/4.2 mg/kg bw/day: ↓bw, ↓bwg, ↓food intake, ↓food efficiency 5.0 mg/kg bw/day: ↓urinary volume, ↑specific gravity (♂) **No evidence of carcinogenicity**
Developmental/Reproductive Toxicity Studies	
1-generation reproductive toxicity (diet) Sprague Dawley rat PMRA #1145977	Supplementary (range-finding) Parental toxicity ≥ 5.9/7.2 mg/kg bw/day: ↓bwg, ↓food intake in 1st week(♂); ↓premating bwg (♀) 9.0/10.5 mg/kg bw/day: ↓food efficiency in 1st week; ↓ gestation and lactation bwg , ↓food intake in 1st week (♀)
2-generation reproductive toxicity (diet) Sprague Dawley rat PMRA #1145978, 1157231	NOAEL = 2/2.5 mg/kg bw/day (♂/♀)(parental and offspring toxicity); > 5.7/7.3 mg/kg bw/day (♂/♀)(reproductive toxicity) Parental toxicity ≥ 5.7/7.3 mg/kg bw/day: ↓bw (P, F1), ↓bwg (P, F1), ↓food intake (P, F1)(♂); ↓bw pre-mating (F1), ↓pre-mating bwg (P, F1), ↓food intake (F1) (♀) Reproductive toxicity None observed Offspring toxicity ≥ 7.3 mg/kg bw/day: ↓bw PND 7, 14, 21, 25 (F1, F2), ↓bwg (F1, F2) **No evidence of sensitivity of the young or reproductive toxicity**
Developmental toxicity (gavage in 1% CMC) Sprague Dawley rat PMRA #1145982	Supplementary (range-finding) Maternal toxicity 5 mg/kg bw/day: ↓bw, ↓bwg during treatment 45 mg/kg bw/day: mortality (1), lethargy (1), loose faeces (1), weight loss during treatment, ↓food intake during treatment, ↑post-implantation loss, ↓placental weight Developmental toxicity 45 mg/kg bw/day: ↑post-implantation loss, ↓fetal bw
Developmental toxicity (gavage in 1% CMC) Sprague Dawley rat PMRA #1145980, 1157232	NOAEL = 4.7 mg/kg bw/day (maternal toxicity); 13 mg/kg bw/day (developmental toxicity) Maternal toxicity ≥ 13 mg/kg bw/day: ↓bwg during treatment, ↓food intake 30 mg/kg bw/day: ↓bw, ↓placental weight Developmental toxicity 30 mg/kg bw/day: ↓fetal bw, ↑small fetuses, ↑space between body wall and organs, ↑ incomplete ossification of supra-occipital bones, sternebral bones, sacral

Study Type / Animal / PMRA #	Study Results
	and caudal vertebrae, metacarpals and metatarsals **No evidence of sensitivity of the young or teratogenicity**
Developmental toxicity (gavage in 1% CMC) NZW rabbit PMRA #1145979	Supplementary (range-finding) Maternal toxicity ≥ 5 mg/kg bw/day: weight loss (GD8) ≥ 10 mg/kg bw/day: weight loss (GD 8,10) 20 mg/kg bw/day: weight loss (GD 6-18), ↓bw (GD18), ↓food intake during treatment Developmental toxicity None observed
Developmental toxicity (gavage in 1% CMC) NZW rabbit PMRA #1145981, 1157233	NOAEL = 5 mg/kg bw/day (maternal , developmental toxicity) Maternal toxicity ≥ 5 mg/kg bw/day: weight loss (GD8), ↓bwg during treatment, slight ↑ late resorptions 15 mg/kg bw/day: ↓fecal output, abortions (1 on day 19, 1 on day 25), weight loss (GD 8, 10, 12 ,14), ↓bw (GD20), ↓bwg during treatment, ↓food intake during treatment Developmental toxicity ≥ 5 mg/kg bw/day: slight ↑ late resorptions 15 mg/kg bw/day: abortions (1 on day 19, 1 on day 25), ↑rib variants **No evidence of sensitivity of the young or teratogenicity**
Developmental toxicity (dermal in 0.5% CMC) Himalayan rabbit PMRA #1164786	NOAEL = 70 mg/kg bw/day (maternal toxicity) NOAEL = 170 mg/kg bw/day (developmental toxicity) Maternal toxicity ≥ 70 mg/kg bw/day: slight eschar ≥ 170 mg/kg bw/day: moderate to severe erythema, slight edema, weight loss during treatment, ↓food intake during treatment 450 mg/kg bw/day: severe erythema and edema Developmental toxicity 450 mg/kg bw/day: ↓fetal weight (♂), ↑incomplete ossification of skull **No evidence of sensitivity of the young or teratogenicity**
Genotoxicity Studies	
DNA damage in E.coli PMRA #1145984	Negative up to 10 mg/mL
Reverse mutation assay S. typhimurium (TA 1535, TA1537,	Negative up to 5 mg/mL

Study Type / Animal / PMRA #	Study Results
TA100, TA98), E. coli (WP2) PMRA #1145985	
Micronucleus test CD-1 mouse PMRA #1145986	140 mg/kg bw: mortality, ↓locomotor activity, ataxia, prone posture, cold to touch – micronuclei not assessed ≤ 65 mg/kg bw: negative
Cytogenetics test Chinese hamster lung cells PMRA #1145987	Negative up to 100 ug/mL without activation or 50 ug/mL with activation
In vitro mammalian cell gene mutation test Chinese hamster V79 cells PMRA #1145988, 1164215	Negative up to 50 ug/mL
Neurotoxicity Studies	
Acute neurotoxicity (gavage) CD rat PMRA #1164216	NOAEL = 44 mg/kg bw ≥ 44 mg/kg bw: ↓food intake on day of treatment ≥ 80 mg/kg bw: hunched posture, piloerection, weak startle reflex and flexor response (1 on day 1) (♂) 200 mg/kg bw: tremors, partially closed eyes, weak flexor response on day 1; ↓bwg days 0-5, slow or poorly coordinated righting reflex on day 1, weak startle reflex (day 1) (♂); hunched posture, piloerection, weight loss days 0-5 (♀)
13-week neurotoxicity (diet) CD rat PMRA #1164797	NOAEL = 8.5/9.3 mg/kg bw/day (♂/♀) 29/31 mg/kg bw/day: ↓bw, ↓bwg, ↓food intake, ↓food efficiency
Developmental neurotoxicity (diet) Sprague Dawley rat PMRA #2294484	NOAEL = 2.2 mg/kg bw/day (maternal and offspring) <u>Maternal toxicity</u> ≥ 4.2 mg/kg bw/day: ↓bw, ↓bwg (during first half of gestation), ↓food intake (gestation and lactation), ↓activity and rearing counts (LD 4 and 11) 8.4 mg/kg bw/day: ↓bwg (during second half of gestation and first week of lactation), slight ↑ in piloerection (LD 4, 11), altered fur condition and/or fur staining (LD 4, 11, 20) and ↓activity (GD 18), marginal shift (↑) in gestation length <u>Offspring toxicity</u> ≥ 4.2 mg/kg bw/day: ↓bw at PND 21, 8.4 mg/kg bw/day: ↓bw at PND 11 through PND 63, ↓bwg (pre-weaning), ↑activity in FOB post-weaning, slight ↑ ambulation (PND 59); slight ↑ ambulation (PND 22), equivocal response on learning and memory (PND 60) (♂); ↑ incidence of vocalization post-weaning during cage-side observation , ↑ rearing in FOB post-weaning, slight ↑ rearing (PND 59)(♀)

Study Type / Animal / PMRA #	Study Results
Other Studies	
13-week study on induction of saliva by capsule Beagle dog PMRA #1145959 (non-guideline)	300 mg/dog/day (stomach soluble capsule): diarrhea and vomiting in first 2 weeks, emaciation (1), weight loss, ↓food intake 300 mg/dog/day (stomach resistant capsule): diarrhea and vomiting in first 2 weeks No salivation reported in either group
Metabolite Studies (PB-7)	
Acute oral toxicity Sprague Dawley rat PMRA #2294508	LD_{50} = 2728 mg/kg bw (♂), 3086 mg/kg bw (♀) (1% CMC) Signs of toxicity included ↓motor activity, ataxia, ungroomed appearance, hunched or prone posture, hyperpnea, hypopnea, tachypnea, bradypnea, piloerection, diarrhea, bloated abdomen, lethargy, blanching, cyanosis, muscle flaccidity, gasping, pupil dilation **Low acute toxicity**
Reverse mutation assay S. typhimurium (TA 1535, TA1537, TA100, TA98), E. coli (WP2) PMRA #2294511	Negative up to 5 mg/mL.
Bacterial DNA damage assay E. coli (WP2, WP67, CM871) PMRA #2294512 (non-guideline)	Negative up to 10 mg/mL. Considered supplemental due to deficient positive control data and non-guideline protocol.

Table 2 Toxicology Endpoints for Use in Health Risk Assessment for Pyridaben

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE[1]
Acute dietary (general population)	Acute oral neurotoxicity – rat	NOAEL = 44 mg/kg bw Clinical signs, weak reflex response	100
	ARfD = 0.4 mg/kg bw		
Repeated dietary (general population)	One-year oral study – dog *Co-critical studies* 78-week dietary oncogenicity – mouse 104-week dietary chronic toxicity/ oncogenicity – rat	NOAEL = 0.5 mg/kg bw/day Clinical signs, reduced weight gain NOAEL = 0.81 mg/kg bw/day Reduced weight gain NOAEL = 1.1 mg/kg bw/day Reduced weight gain and food intake	300
	ADI = 0.0017 mg/kg bw/day		
Dermal – all durations	Three-week dermal study – rat	NOAEL = 100 mg/kg bw/day Reduced weight gain	300
Inhalation – all durations	Four-week inhalation study – rat	NOAEL = 0.78 mg/kg bw/day Reduced weight gain	300
Cancer	No evidence of carcinogenicity – assessment not required		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Protection factors* for dietary assessment. MOE refers to a target MOE for occupational and residential assessment

Appendix V Dietary Exposure and Risk Estimates for Pyridaben

Table 1. Acute Dietary Exposure and Risk Estimates for Pyridaben

	Acute exposure (95th percentile)			
	Food only		Food + water	
	Exposure	%aPAD	Exposure	%aPAD [1]
General Population	0.003892	4	0.003968	4
All infants (< 1 year old)	0.019260	19	0.019311	19
Children 1-2 years	0.010987	28	0.011038	28
Children 3-5 years	0.007826	19	0.007876	19
Children 6-12 years	0.004802	11	0.004853	11
Youth 13-19 years	0.002769	6	0.002870	6
Adults 20-49 years	0.002386	5	0.002463	5
Adults 50+ years	0.002074	5	0.002040	5
Females 13-49 years	0.002809	6	0.002860	6

[1] aPAD = 0.1 mg/kg bw

Table 2. Chronic Dietary Exposure and Risk Estimates for Pyridaben

	Chronic exposure			
	Food only		Food + water	
	Exposure	%cPAD	Exposure	%cPAD [1]
General Population	0.000761	38	0.000870	43
All infants (< 1 year old)	0.000182	9	0.000283	14
Children 1-2 years	0.000158	8	0.000167	8
Children 3-5 years	0.000120	6	0.000170	9
Children 6-12 years	0.000080	4	0.000089	4
Youth 13-19 years	0.000056	3	0.000092	5
Adults 20-49 years	0.000070	4	0.000098	5
Adults 50+ years	0.000053	3	0.000070	4
Females 13-49 years	0.000088	4	0.000096	5

[1] cPAD = 0.002 mg/kg bw/day

Appendix VI Food Residue Chemistry Summary

6.1 Summary

Pyridaben [2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3(2H)-one] is a selective miticide and insecticide used for the control of a wide range of insect species in orchards, vineyards and greenhouses. In Canada, pyridaben is currently registered for use on apple, cherry (sweet and tart), grape, nectarine and peach (Ontario only), pear, raspberry (post-harvest application only), strawberry, greenhouse cucumber, greenhouse pepper and greenhouse tomato.

The most recent dietary risk assessment for pyridaben was conducted in 2013. For the purposes of re-evaluation, the dietary exposure assessment was updated to include the revised toxicological reference doses, an exposure adjustment factor (EAF) to estimate residues of pyridaben metabolites in plant commodities, recent food surveillance data, use information and crop production data.

The residue chemistry database was found to be complete and adequate for risk assessment purposes. Submitted residue chemistry studies have been reviewed and found sufficient to support current registrations. The nature of the residue in livestock and plant commodities is adequately understood based on acceptable metabolism studies in lactating goats, laying hens, apple, citrus, eggplant and tomato which indicate that pyridaben is highly metabolized.

Maximum residue limits are established under the *Pest Control Product Act* and can be found in PMRA's MRL database. Pyridaben MRLs are also listed in Appendix VIII. The residue definition for enforcement in plant and animal commodities is currently expressed as the parent pyridaben. The residue definition for the risk assessment is the parent pyridaben for animal commodities, and pyridaben and all the metabolites containing the pyridazinone ring for all plant commodities.

PMRA has calculated an EAF of 1.48 to estimate pyridaben metabolites in plant commodities. The EAF is the ratio of residues containing the pyridazinone ring to pyridaben derived from the low dose pyridaben apple and orange metabolism studies.

Analytical methods, storage stability, magnitude of residue data and processed food studies have been found to be adequate. Due to updated methods for calculating livestock dietary burden, the livestock dietary burden has been reassessed to evaluate potential secondary residues of pyridaben in/on livestock commodities from consumption of feed items with pyridaben residues resulting from the treated food/feed commodities (such as wet apple pomace).

Acute, chronic aggregate (food + water) dietary exposure assessments were conducted for pyridaben using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 2.14) program which incorporates consumption data from the USDA Continuing Surveys of Food Intakes by Individuals, 1994-1996 and 1998. PMRA has concluded that the risk from dietary exposure to pyridaben is not of concern.

6.2 Metabolism

The metabolic pathway of pyridaben consists of four routes: rearrangement, side chain oxidation, splitting into benzyl, and pyridazinone moiety. The main difference between plants and animals is the existence of a photodegradation route in plants. Characterization of the metabolites indicates a photochemical rearrangement of pyridaben to yield a thiol, which dimerizes to a transient metabolite, D-1, and undergoes further reaction including oxidation as well as an alternate pathway involving oxidation of the methyl moieties. Metabolism and transformation studies revealed that pyridaben undergoes transformations in the sunlight range (>290 nm) indicating that photo-transformation (photolysis) would be a significant route.

The names of the pyridaben metabolites and their chemical names are presented in Table 1. Metabolites were identified as containing one or both rings by the use of the prefixes PB, P (pyridazinone), or B (benzyl). PB-1 is the parent, P-# is a metabolite containing only the pyridazinone ring and B-# is a metabolite containing only the benzyl ring.

Table 1 Pyridaben Metabolites and their Chemical Names

Metabolite	Chemical Name
PB-1	2-*tert*-butyl-5-(4-*tert*-butylbenzylthio)-4-chloropyridazin-3(*2H*)-one
PB-3	2-*tert*-butyl-5-(4-*tert*-butylbenzylsulfonyl)-4-chloropyridazin-3(*2H*)-one
PB-4	2-*tert*-butyl-5-(4-*tert*-butylbenzylsulfinyl)-4-chloropyridazin-3(*2H*)-one
PB-7	2-*tert*-butyl-5-[4-(1-carboxy-1-methylethyl)benzylthio]-4-chloropyridazin-3(*2H*)-one
PB-9	2-*tert*-butyl-4-chloro-5-[4-(1,1-dimethyl-2-hydroxyethyl)benzylthio]-chloropyridazin-3(*2H*)-one
PB-11	5-(4-*tert*-butylbenzylthio)-4-chloro-2-(1,1-dimethyl-2-hydroxyethyl)pyridazin-3(*2H*)-one
PB-12	5-(4-tert-butylbenzylthio)-2-(1-carboxy-1-methylethyl)-4-chloropyridazin-3(*2H*)-one
PB-13	4-chloro-2-(1,1-dimethyl-2-hydroxyethyl)-5-[4-(1,1-dimethyl-2-hydroxyethyl)benzylthio-pyridazin-3(*2H*)-one
PB-14	2-tert-butyl-4-(4-tert-butylbenzyl)pyridazin-3(*2H*)-one-5-sulfonic acid
PB-15	2-tert-butyl-4-(4-tert-butylbenzyl)5-mercapto-pyridazin-3(*2H*)-one
PB-17	2-tert-butyl-4-(4-tert-butylbenzyl)-pyridazin-3(*2H*)-one
PB-22	2-tert-butyl-4-(4-tert-butylbenzoyl)-pyridazin-3(*2H*)-one-5-sulfonic acid
P-1	2-*tert*-butyl-4-chloro-5-mercaptopyridazin-3(*2H*)-one
P-3	2-*tert*-butyl-4-chloro-5-hydroxypyridazin-3(*2H*)-one
P-14	2-tert-butyl-4-chloropyridazin-3(2H)-one-5-sulfonic acid
P-16	4-chloropyridazin-3(2H)-one-5-sulfonic acid
D-1	di-[2-tert-butyl-4-(4-tert-butylbenzyl)pyridazin-3(2H)-one-5-yl]disulfide
D-2	5,5'-Dithiobis[2-tert-butyl-4-chloropyridazin-3 (2H)-one]
D-3	2,7-di-tert-butyldipyridazo[4,5-6 4,4',5'-e]-1,4-dithiin-1,6(2H,7H)dione
D-6	di-(4-tert-butylbenzyl)disulfide

Metabolite	Chemical Name
B-1	4-*tert*-butylbenzoic acid
B-3	4-*tert*-butylbenzyl alcohol
B-7	2-(4-carboxyphenyl)-2-methylpropionic acid
B-8	2-(4-hydroxymethylphenyl)-2-methyl-1-propanol
B-11	2-(4-carboxyphenyl)-2-methyl-1-propanol
W-1	3,6-di-tert-butyl-4-oxo-3H,9H-10-thia-2,3-diazaphenanthrene

6.2.1 Plant Metabolism

The nature of pyridaben residues in the registered crops is adequately understood based on the submitted pyridaben metabolism studies in apples, eggplants and oranges. A tomato metabolism reviewed by the European Food Safety Authority (EFSA) showed a similar metabolic pathway. The submitted studies cover the metabolism requirements for the registered crops.

Following plant application, pyridaben was the major metabolite identified. Pyridaben residues rapidly dissipated after application via photo-induced rearrangement. Pyridaben broke down to a multitude of metabolites with several metabolites containing either the pyridazinone (PB) or phenyl (benzyl; B) ring which generally sum up to more than 10% of the total radioactive residues. The minor metabolites include: PB22, PB14, PB17, B1 and B4 (see enclosed table for metabolite description).

Due to the structural similarity with the parent compound, it was considered that the metabolites containing the PB ring may have a comparable toxicity with the parent. Furthermore, there is no evidence to discount the relevance and the risk potential of the PB metabolites; therefore, the organo-soluble PB metabolites were included in the exposure and risk assessment. To account for the potential exposure to the PB metabolites, an EAF of 1.48 was determined from the low-dose apple and orange metabolism studies and included in the exposure determination (see Table 2).

Table 2 Determination of the Exposure Adjustment Factor

%TRR	Oranges (Hamlin)		Oranges (Valencia)		Apple
	Bz label	Pz label	Bz label	Pz label	
PB-1	23.24	12.56	13.52	23.22	20.8
PB-11		0.38		4.09	
PB-14	4.55	4.21	1.79	1.53	
PB-22	1.38	2.31	0.51	0.37	
B1+PB-11	1.85		4.08		
B3 + unknown	0.62				
B-11	2.73		0.66		
P-14		3.61		0.32	
Pyridazinone	7.78	10.51	6.38	6.31	8.7

%TRR	Oranges (Hamlin)		Oranges (Valencia)		Apple
	Bz label	Pz label	Bz label	Pz label	
PB-1 + PYR / PYD	1.33	1.84	1.52	1.27	1.42
Average	1.585		1.395		1.42
	Mean average : orange				
	1.49				
	Apple-Orange average ratio				
	1.48				

6.2.2 Animal Metabolism

The qualitative nature of the pyridaben residues in livestock has been studied and is adequately understood. The metabolism studies were conducted by oral administration of radiolabelled pyridaben in ruminant and poultry.

Metabolic pathways in rats and goats are nearly identical. The metabolism of pyridaben is not only extensive but rapid with no accumulation of residues in tissues. The primary route of excretion is via the feces with, however, a significant amount of pyridaben and/or intestinal metabolites absorbed. The primary detoxification mechanism is oxidation of the benzyl t-butyl group to corresponding alcohol and carboxyl groups, followed by biliary excretion. Oxidation of the pyridazinone t-butyl group does not appear to be as important as the benzyl t-butyl group, in that the corresponding metabolites are found at much lower concentrations.

In ruminants, metabolites identified included B-11, PB-7, B-1, B-7, B-8 and PB-13. No more than 0.4% of the cumulative dose was found in the total tissue. Only the liver sample contained enough radioactivity for extensive metabolite identification work. In liver, the parent pyridaben was the only major residue, whereas metabolites PB-7 and PB-9 were found as minor metabolites. No specific residue was firmly identified in other tissues or in milk. The total radioactive residues (TRRs) in those commodities were low in actual value but represent a high percentage of the administered TRR. For the present assessed use pattern the metabolism data provided is satisfactory but further residue identification may be required for any use expansions of pyridaben.

The metabolism study using laying hens indicated low residues in tissues. In liver, PB-7 is the major metabolite and parent pyridaben was not found. The fat and skin were found to contain pyridaben and PB-7 and PB-9. No specific residue was firmly identified in other tissues.

6.2.3 Residue Definition

The qualitative nature of pyridaben residues in plant and animal is well understood based on reviews of acceptable plant and animal metabolism studies. The parent pyridaben was the single common major metabolite in all commodities. Following the re-evaluation process, no modifications are necessary to the residue definition for MRL setting and enforcement purposes, which is the parent pyridaben. The residue definition for the risk assessment included the parent pyridaben for animals, and pyridaben and all metabolites containing the pyridazinone ring for plants.

6.3 Analytical Methods

Two gas chromatography methods with electron capture detection were developed, validated and used for data gathering and enforcement purposes. These methods are designated as BASF D9309 and D9312 (with some variants) and are found suitable for the determination of pyridaben residues in plant commodities. The validated BASF GC-ECD method D9405 determines residues of pyridaben and its metabolites PB-7 and PB-9 in animal matrices.

A multi-residue method for pyridaben and its metabolites has not been submitted by the registrant. The Food and Drug Administration multi-residue screening methods are not applicable for the analysis of pyridaben, PB-7 and PB-9 metabolites residues, because the chemicals do not produce sufficient response on any of the gas chromatography systems at standard conditions.

6.4 Food Residues

6.4.1 Storage Stability

PMRA has concluded that pyridaben residues are stable in fruits, vegetables and animal food commodities under frozen storage for at least six months in plant commodities and for up to five months in animal commodities. Submitted studies included almond nutmeat and hulls; apples, dry pomace and apple juice; grapes; oranges and orange juice; plums and prunes; and cherries. For animals, storage stability in cow muscle and milk samples was demonstrated for at least five months.

6.4.2 Crop Residues

Crop residue data were available from registrant submitted field trial studies, the Canadian Food Inspection Agency (CFIA) pesticide monitoring program and the United States Department of Agriculture Pesticide Data program pesticide monitoring program.

Field Trial Residue Data

A large database of field trial studies was submitted and reviewed. The submitted studies cover a large range of application rates, pre-harvest intervals, crops and growing zones that are more or less adequate to the registered Canadian and American usage of pyridaben; therefore, only the appropriate residue value was selected to be used in the determination of the magnitude of residues in the various commodities.

A summary of the residue data in the registered commodities (Canada and United States) determined as highest average field trial (HAFT) and supervised trial median residue for the trials performed at or near Canadian Good Agricultural Practices (GAP) is presented below. Field trial data from climatic zones outside of Canada and at rates higher than the Canadian GAP are included only where they represent the best available data.

Table 3 Pyridaben Residues in Plant Commodities

Commodity	Residues (ppm)			
	Mean	Median	HAFT	Max
Almonds	0.05	0.05	0.05	0.05
Apple	0.22	0.22	0.44	0.44
Cherry	0.51	0.40	1.08	1.28
Cranberries	0.31	0.30	0.40	0.45
Grapes	0.51	0.35	1.38	1.38
Orange	0.09	0.08	0.37	0.37
Grapefruit	0.14	0.12	0.24	0.24
Lemon	0.33	0.35	0.42	0.42
Hops	6.69	7.38	8.28	8.49
Peach	0.33	0.22	1.61	1.61
Pear	0.29	0.26	0.58	0.58
Plum	0.12	0.05	0.46	0.46
Strawberry	1.00	0.93	2.19	2.19
GH cucumber	0.11	0.10	0.19	0.19
GH tomato	0.43	0.39	1.1	1.1
GH green beans	0.07	0.06	0.1	0.1
GH eggplant	0.08	0.08	0.08	0.08
GH melon	0.05	0.05	0.05	0.05
GH pepper	0.07	0.07	0.09	0.09

CFIA Residue Monitoring Data

A summary of CFIA and United States Department of Agriculture Pesticide Data program monitoring residue values, determined for the last 5 years and employed in the dietary risk assessment, is presented in Table 1, Appendix VII. The monitoring data used consists of over 6200 CFIA and 10500 United States Department of Agriculture Pesticide Data Program samples analyzed for a large number of domestic and imported commodities.

6.4.3 Livestock Residues

A ruminant feeding study was reviewed to determine residues in milk and tissues. For 29 days, lactating cows were administered pyridaben at a dose level of 2.5 ppm (United States anticipated dietary intake from proposed United States usage) and at the exaggerated dose levels of 7.5 and 25 ppm. Milk samples were collected twice each day and combined as one aliquot. Samples were analyzed by BASF analytical method D9406. A summary of the results are presented in Table 4.

Table 4 Summary of Residues of Pyridaben and its Metabolites in Ruminants

Commodities	Maximum Residue (ppm) at Dose Level		
	1x : 2.5 ppm	3x : 7.5 ppm	10x : 25 ppm
Milk	< 0.01	< 0.01	0.028 (Pyridaben)
Liver	< 0.05	0.051 (PB-7)	0.15 (PB-7)
Muscle	< 0.05	< 0.05	< 0.05
Kidney	< 0.05	< 0.05	< 0.05
Fat	< 0.05	< 0.05	0.08 (Pyridaben)

Maximum Theoretical Dietary Burden (MTDB)

Based on residues of plant commodities, MTDB was determined for the labelled use of pyridaben. The MTDB represents an upperbound estimate of potential residues of a pesticide in treated feed that could then be consumed by animals (such as cattle, poultry), which in turn would result in commodities (such as meat, dairy, eggs) that would be consumed by humans. For pyridaben, the only potential treated feed item is wet apple pomace which could be fed to dairy cattle. By using the apple wet pomace residue value of 0.5 ppm (Canadian MRL for apple), and assuming that 10% of the cow's diet consists of wet apple pomace, the dietary burden (or estimated amount of pyridaben in the feed) is 0.12 ppm (Table 5). The PMRA then uses the results of livestock feeding studies to estimate residues in animal commodities that humans would consume. For pyridaben, since no residues were detected in animals treated at the 2.5 ppm dose level, the PMRA does not expect any detectable residues in tissues when animals are given residues in feed at the dietary burden level of 0.12 ppm.

Table 5 Determination of the Dietary Burden in Dairy Cattle

Dairy cattle							
Crop	Commodity	Type	Residue		% dry matter	% diet	Dietary contribution (ppm)
			ppm	Input			
Apple	Pomace, wet	Carbohydrate Concentrate	0.5	MRL	40	10	0.12

6.4.4 Confined and Field Crop Rotation

There are no confined crop or field crop rotational studies available on file as the registered crops are either established crops or crops that do not require such studies.

PMRA notes that both EFSA and USEPA have reviewed such studies and these data may be required for use expansions, if applicable.

6.4.5 Processing Factors

Many treated raw agricultural commodities may be processed, which could concentrate or dilute the residues (for example, apple to apple juice). Processing studies are conducted to determine the degree of change in residues following processing. Food processing studies were submitted for apple, grape, orange and plum. Studies for the fate of the residues following consumer practices or industrial processing were submitted and reviewed by PMRA. The results are summarized in Table 2, Appendix VII.

6.4.6 Domestic Production, Imports and Percentage of Treated Crops

In the absence of information on the extent of use of pyridaben for specific commodities, the PMRA assumes that all samples of a specific commodity may have been treated with the given pesticide (100% crop treated). When there is a possibility that some food commodities may not have been treated, residue distribution or levels may be adjusted using percent crop treated (%CT) information. Percent CT should reflect current use patterns. Percent CT data is applied to residue estimates derived from field trial data. For surveillance data, %CT data may be used to refine estimates for specific commodities with a large number of non-detect residues.

Percent CT data and domestic production and import statistics were used to refine the exposure estimates for the chronic scenario. To define the percent crop treated of all foods consumed by Canadians, defined as the Canadian Weighted Percent Crop Treated, one requires the percent crop treated of food grown in Canada and of foods grown outside of Canada which may be imported into Canada. As well, one needs to know the ratio of domestic production of foods in Canada compared to the amount of that food that is imported from various countries.

For all commodities, a Canadian Weighted Percent Crop Treated value was calculated according to the following formula below:

Canadian Weighted %CT
= (%CT Canada × % domestic production) + (%CT in the United States × % the United States crops imported) + (%CT in other countries × % imports from other countries)

Appendix VII Residue Data Used in the Chronic Dietary Analysis

Table 1 CFIA and USDA PDP Monitoring Residue Data

Food commodity	CDN US	CFIA 2008 - 2010				PDP 2008 – 2011	
		Domestic		Imports			
		# detects / # samples	Residue (ppm)	# detects / # samples	Residue (ppm)/ Country	# detects / # samples	Residue (ppm)/ Country
Apple	Y Y	*7 / 665*	0.0067, 0.0118, 0.0299, 0.0038, 0.0105, 0.0117 and 0.0334	*4 / 404*	0.0033, 0.0055, 0.0084 and 0.0146 - the United states	*1 / 210*	0.025 - the United States
Apricot	N Y	0 / 57		0 / 49		NA	
Cherries (sweet and tart)	Y Y	0 / 55		0 / 107		NA	
Citrus	N Y	-					
Grapefruit		-		0 / 251		NA	
Lemon		-		0 / 219		NA	
Lime		-		0 / 175		NA	
Orange		-		*5 / 711*	0.0055, 0.0355, 0.0027, 0.0102 and 0.0106 - the United States	0 / 1448	
Tangerine		-		NA			
Cranberries	N Y	0 / 21		0 / 19		NA	
Cucumber (GH)	Y N	0 / 83		0 / 53 (0/205 fresh)		0 / 582 (fresh)	
Grape	Y Y	0 / 35		*1 / 508*	0.4158 - the United States	*4 / 1467*	0.05, 0.059, 0.18 and 0.19 - the United States
Hop	N Y	NA		NA		NA	
Nectarines	Y Y	0 / 44		0 / 105		0 / 672	
Mango	N			0 / 168			
Papaya	N			0 / 128			
peaches	y y	0 / 77		0 / 129		*2 / 616*	0.059 – chile 0.017 - the United States
Pears	Y Y	*2 / 83*	0.018 and 0.02	*2 / 415*	0.0205 and	*8 / 1473*	0.07 (x5), 0.0704 (x2)

Food commodity	CDN US	Domestic	CVIA 2008 - 2010	Imports		PDP 2008 – 2011	
		# detects / # samples	Residue (ppm)	# detects / # samples	Residue (ppm)/ Country	# detects / # samples	Residue (ppm)/ Country
					0.0275 - the United States		and 0.17 - the United States
Pepper (GH)	Y	0 / 91		0 / 118		*1 / 1485*	0.0044 – Dominican Rep
Pistachio	N Y	-		NA		NA	
Plums	N Y	0 / 51		0 / 120		0 / 143	
Prunes	N Y	NA		NA		NA	
Raspberries	Y N	0 / 19		0 / 94		NA	
Strawberries	Y Y	0 / 49		0 / 283		0 / 1485	
Tomato (GH)	Y Y	2 / 96	0.005 and 0.055	*4 / 432 (fresh)*	0.069 – Belgium 0.0223 – Mexico 0.0128 and 0.0212 - Spain	*2 / 740 (fresh)*	0.06 – Mexico 0.06 - the United States
Tree nut group (almond, beech, Brazil, buttermut, cashew, chestnut, chinquapin, filbert, hickory, macadamia, pecan, black walnut and English walnut)	N Y	NA		NA		Almond : 0 / 185	
Tropical fruits (papaya, black sapote, mango, sapodilla, mamey sapote and canistel)	N Y			Mango : 0 / 168 Papaya : 0 / 128			
Commodities Not Registered in Canada or the the United States with Detects							
Bok Choy, fresh					0.0439 - China		
Yu choy, fresh				1 / 2	0.0126 - China		

Table 2 Processing Factors for Plant Commodities Used in the Chronic Exposure Assessment

Commodity	DEEM Food Form	Processing Factor	Representative Crop
Apple	Fruit with peel	1	Apple fresh
	Peeled fruit	1	Apple fresh
	Peeled fruit baby food	1	Apple fresh
	Dried	8(Default)	Apple fresh
	Dried baby food	8(Default)	Apple fresh
	Juice	0.1	Apple fresh
	Juice baby food	0.1	Apple fresh
	Sauce	1	Apple fresh
	Sauce baby food	1	Apple fresh
Apricot	Apricot	1	Peach
	Baby food	1	Peach
	Dried	6 (Default)	Peach
	Juice	1	Peach
	Juice baby food	1	Peach
Cherry	Cherry	1	Cherry, fresh
	Baby food	1	Cherry, fresh
	Juice	1.5 (Default)	Cherry, fresh
	Juice baby food	1.5 (Default)	Cherry, fresh
Cucumber GH	Cucumber	1	Cucumber GH
Grape	Grape	1	Grape, fresh
	Juice	0.06	Grape, fresh
	Juice baby food	0.06	Grape, fresh
	Leaves	1	Grape, fresh
	Raisin	0.8	Grape, fresh
	Wine and sherry	1	Grape, fresh
Nectarine	Nectarine	1	Nectarine, fresh
Mango	Mango	1	Mango, fresh
	Baby food	1	Mango, fresh
	Dried	1	Mango, fresh
	Juice	1	Mango, fresh
	Juice, baby food	1	Mango, fresh
Olive	Olive	1	Olive
	Oil	1	Olive
Papaya	Papaya	1	Papaya, fresh
	Baby food	1	Papaya, fresh
	Dried	1.8	Papaya, fresh
	Juice	1.5	Papaya, fresh
Peach	Peach	1	Peach, fresh
	Baby food	1	Peach, fresh
	Dried	7	Peach, fresh
	Dried baby food	7	Peach, fresh
	Juice	1	Peach, fresh
	Juice baby food	1	Peach, fresh

Commodity	DEER Food Form	Processing Factor	Representative Crop
Pear	Pear	1	Pear, fresh
	Baby food	1	Pear, fresh
	Dried	6.25	Pear, fresh
	Juice	0.1	Pear, fresh
	Juice, baby food	0.1	Pear, fresh
Pepper Gbl	Bell	1	Pepper Gbl fresh Pepper fresh
	Baby food	1	Pepper Gbl fresh Pepper fresh
	Dried	1	Pepper Gbl fresh Pepper fresh
	Baby food	1	Pepper Gbl fresh Pepper fresh
	Non bell	1	Pepper Gbl fresh Pepper fresh
	Baby food	1	Pepper Gbl fresh Pepper fresh
Plum	Plum	0.8	Plum, fresh
	Baby food	0.8	Plum, fresh
	Prune, fresh	0.8	Plum, fresh
	Baby food	0.8	Plum, fresh
	Prune, dried	3.1	Plum, fresh
	Prune, juice	0.8	Plum, fresh
	Baby food	0.8	Plum, fresh
Raspberry	Raspberry	1	Raspberry, fresh
	Baby food	1	Raspberry, fresh
	Juice	1	Raspberry, fresh
	Juice, baby food	1	Raspberry, fresh
Strawberry	Strawberry	1	Strawberry, fresh
	Baby food	1	Strawberry, fresh
	Juice	1	Strawberry, fresh
	Juice, baby food	1	Strawberry, fresh
Tomato	Tomato	1	Tomato, fresh
	Baby food	1	Tomato, fresh
	Paste	5.4	Tomato, paste
	Paste, baby food	5.4	Tomato, paste
	Puree	3.3	Tomato, paste
	Puree, baby food	3.3	Tomato, paste
	Dried	14.3	Tomato, fresh
	Dried, baby food	14.3	Tomato, fresh
	Juice	1.5	Tomato, fresh
Citrus	Citrus	1	Orange
	Hybrids	1	Orange
Grapefruit	Grapefruit	1	Grapefruit
	Juice	0.1	Orange juice
Lemon	Lemon	1	Lemon
	Juice	0.1	Orange juice
	Juice, baby food	0.1	Orange juice

Commodity	DEER Food Form	Processing Factor	Representative Crop
	Fruit	1	Lemon
Lime	Lime	1	Lime
	Juice	0.1	Orange juice
	Juice, baby food	0.1	Orange juice
Orange	Orange	1	Orange
	Juice	1	Orange juice
	Juice, baby food	1	Orange juice
	Fruit	1	Orange
Tangerine	Tangerine	1	Tangerine
	Juice	0.1	Orange juice
Almond	Almond	1	Almond
	Oil	1	Almond
Pistachio		1	Almond
All other tree nuts Brazil nut Butternut Cashew Chestnut Filbert Macadamia Pecan Walnut		1	Almond

Appendix VIII Supplemental Maximum Residue Limit Information - International Situation and Trade Implications

Maximum residue limits may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

The tables below list current Canadian MRLs and American tolerances, as well as applicable residue definitions. No MRLs were established by the Codex Alimentarius Commission.

Table 1 Canadian MRLs and US Tolerances

Food Commodity	Canadian MRL (ppm)	US Tolerance (ppm)
Almond, nuts	0.05	
Apple	0.5	0.5
Apple, wet pomace		0.75
Canistel		0.10
Cattle, fat		0.05
Cattle, meat	0.05	0.05
Cattle, meat byproduct		0.05
Citrus		0.5
Citrus, dried pulp		1.5
Cucumber	0.1	
Fruit, stone		2.5
Goat, fat		0.05
Goat, meat	0.05	0.05
Goat, meat byproducts		0.05
Grape	0.3	1.5
Hog, fat		0.05
Hog, meat		0.05
Hog, meat byproducts		0.05
Hop, dried cones		10.0
Horse, fat		0.05
Horse, meat	0.05	0.05
Horse, meat byproducts		0.05
Mango		0.10
Milk	0.01	0.01
Nectarine	1.5	Fruit, stone
Nut, tree, group 14		0.05
Papaya		0.10

Food Commodity	Canadian MRL (ppm)	US Tolerance (ppm)
Peach	1.5	Fruit, stone
Pear	0.75	0.75
Peppers	1	
Pistachio		0.05
Sapodilla		0.10
Sapote, black		0.10
Sapote, mamey		0.10
Sheep, fat		0.05
Sheep, meat	0.05	0.05
Sheep, meat byproducts		0.05
Star apple		0.10
Strawberry	2	2.5
Sweet cherries	1.3	
Tart cherries	1.3	
Tomato	0.15	0.15
Tolerances with regional registration, as defined in § 180.1(m) are established for residues of the insecticide pyridaben [2-tert-butyl-5(4-tert-butylbenzylthio)-4-chloropyridazin-3(2H)-one] in or on the following raw agricultural commodity:		
Cranberry		0.5

Table 2 Residue Definition in Canada and Other Jurisdictions

Residue definition	Canada	US	Codex
Enforcement	Parent pyridaben [2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3(2H)-one]	US Tolerances are established for residues of the parent pyridaben [2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3(2H)-one] in plants, and of the insecticide pyridaben and its metabolites (2-tert-butyl-5-(4-(1-carboxy-1-methylethyl)benzylthio)-4-chloropyridazin-3(2H)-one] and (2-tert-butyl-5-[4(-1,1-dimethyl-2-hypdroxyethyl)benzylthio-4-chloropyridazinn-3(2H)-one) in animals	No MRLs or residue definition established
Risk Assessment	Parent pyridaben and metabolites containing the pyridazinone ring for plant commodities and parent pyridaben for animal commodities	Parent pyridaben and metabolites containing the pyridazinone ring for plant commodities and parent pyridaben plus its metabolites (2-tert-butyl-5-(4-(1-carboxy-1-methylethyl)benzylthio)-4-chloropyridazin-3(2H)-one] and (2-tert-butyl-5-[4(-1,1-dimethyl-2-hypdroxyethyl)benzylthio-4-chloropyridazinn-3(2H)-one) for animal commodities	N/A

Appendix IX Occupational Risk Assessments PROTECTIVE

Table 1 Mixer/Loader/Applicator Exposure Estimates and MOEs with Baseline Personal Protective Equipment

Crop	Form [1]	Application Equipment [2]	Application Rates [3] (kg a.i./L) or (kg a.i./ha)	Area Treated per Day [4] (ha) or (L)	Daily Exposure (µg/kg/day)		Margins of Exposure		
					Dermal [5]	Inhalation [6]	Dermal [7]	Inhalation [8]	Combined [9]
Apples, Cherries (sweet and tart), Peaches, Nectarines, Grapes	WSP	airblast	0.45 (kg a.i./ha)	20	65.63	0.07	1524	11594	1347
Pears	WSP	airblast	0.54 (kg a.i./ha)	20	78.75	0.08	1270	9662	1122
Strawberries, Raspberries	WSP	groundboom	0.45 (kg a.i./ha)	26	7.91	0.08	12639	46784	9951
		airblast		20	65.63	0.07	1524	11594	1347
		backpack	9.00E-04 (kg a.i./L)	150 L	9.19	0.01	10882	74432	9494
		MP HW			1.59	0.01	62817	102262	38913
Outdoor Ornamentals(nursery)	WSP	backpack	8.40E-04 (kg a.i./L)	150 L	8.58	0.01	11659	79748	10172
		MP HG		3800 L	222.86	0.60	449	1295	333
		MP HW		150 L	1.49	7.12E-03	67303	109566	41693

[1,2] WSP = Wettable Powder in Water Soluble Packaging, MP HG = mechanically-pressurized hand held spray gun, MP HW = manually-pressurized hand held spray wand

[3] Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha) or kilograms of active ingredient per litre (kg a.i./L) using the minimum recommended spray volume.

[4] Based on standard assumptions derived from survey data.

[5] Where dermal exposure µg/kg/day = unit exposure x area treated x rate)/80 kg bw.

[6] Where inhalation exposure µg/kg/day = (unit exposure x area treated x rate)/80 kg bw; includes a 90% protection factor for respirators.

[7] Based on a dermal NOAEL of 100 mg/kg bw/day and a target dermal MOE of 300. Shaded cells indicate those MOEs that do not reach the target of 300.

[8] Based on an inhalation NOAEL of 0.78 mg/kg bw/day and a target inhalation MOE of 300.

[9] Combined MOE = 1 ÷ ((1 ÷ Dermal MOE) + (1 ÷ Inhalation MOE)). Target MOE = 300.

Table 1 Mixer/Loader/Applicator Exposure Estimates and MOEs with Baseline Personal Protective Equipment (continued)

Crop	Form [1]	Application Equipment [2]	Application Rates [3] (kg a.i./L) or (kg a.i./ha)	Area treated per day [4] (ha) or (L)	Daily Exposure (µg/kg/day)		Margins of Exposure		
					Dermal [5]	Inhalation [6]	Dermal [7]	Inhalation [8]	Combined [9]
Greenhouse Cucumbers	WSP	mistblower (auto)	2.10E-03 (kg a.i./L)	5000 L	2.84	2.36E-03	3527	330159	31855
		mistblower (hh)		n/a					
		backpack		150 L	21.44	0.02	4664	31899	4069
		MP HG		3800 L	557.15	1.51	179	518	133
		MP HW		150 L	3.72	0.02	26921	43826	16677
Greenhouse Peppers	WSP	mistblower (auto)	8.40E-03 (kg a.i./L)	5000 L	1.14	9.5E-04	88143	825397	79638
		mistblower (hh)		n/a					
		backpack		150 L	8.58	9.78E-03	11659	79748	10172
		MP HG		3800 L	222.86	0.60	449	1295	333
		MP HW		150 L	1.49	7.12E-03	67303	109566	41693
Greenhouse Tomatoes	WSP	mistblower (auto)	1.05E-03 (kg a.i./L)	5000 L	1.41	1.18E-03	70514	660317	63711
		mistblower (hh)		n/a					
		backpack		150 L	10.72	0.01	9327	63799	8137
		MP HG		3800 L	278.58	0.75	359	1036	267
		MP HW		150 L	1.86	8.90E-03	53843	87653	33354
Greenhouse Ornamentals	WSP	mistblower (auto)	1.05E-03 (kg a.i./L)	5000 L	1.93	1.61E-03	51776	484848	46780
		mistblower (hh)		n/a					
		backpack		150 L	14.60	0.02	6849	46845	5975
		MP HG		3800 L	379.39	1.03	264	760	196
		MP HW		150 L	2.53	0.01	39535	64360	24491

[1,2] WSP = Wettable Powder in Water Soluble Packaging; MP HG = mechanically-pressurized hand held spray gun; MP HW = manually-pressurized hand held spray wand; hh = hand held.
[3] Maximum listed label rate in kilograms of active ingredient per litre (kg a.i./L) using the minimum recommended spray volume.
[4] Based on standard assumptions derived from survey data.
[5] Where dermal exposure µg/kg/day = unit exposure x area treated x rate)/80 kg bw.
[6] Where inhalation exposure µg/kg/day = (unit exposure x area treated x rate)/80 kg bw; includes a 90% protection factor for respirators.
[7] Based on a dermal NOAEL of 100 mg/kg bw/day and a target dermal MOE of 300. Shaded cells indicate those MOEs that failed to reach the target of 300.
[8] Based on an inhalation NOAEL of 0.78 mg/kg bw/day and a target inhalation MOE of 300.
[9] Combined MOE = 1 ÷ ((1 ÷ Dermal MOE) + (1 ÷ Inhalation MOE)). Insufficient data exists to assess hand held mistblowers. Shaded cells indicate those MOEs that do not to reach the target of 300.

Table 2 Greenhouse Mixer/Loader/Applicator Exposure Estimates and MOEs with Maximum Personal Protective Equipment

Crop	Form [1]	Application Equipment [2]	Application Rates [3] (kg a.i./L) or (kg a.i./ha)	Area treated per day [4] (ha) or (L)	Daily Exposure (µg/kg/day)		Margins of Exposure		
					Dermal [5]	Inhalation [6]	Dermal [7]	Inhalation [8]	Combined [9]
Greenhouse Cucumbers (spray volume: 500L)	WSP	mistblower (auto)	2.10E-03 (kg a.i./L)	5000 L	7.92	2.36E-03	9200	330159	74494
		mistblower (hh)		n/a					
		backpack		150 L	10.23	0.02	9779	31899	7485
		MP HG		3800 L	244.74	1.51	409	518	228
		MP HW		150 L	2.90	0.02	34543	43826	19317
Greenhouse Cucumbers (spray volume: 1000L)	WSP	mistblower (auto)	1.05E-03 (kg a.i./L)	5000 L	0.52	1.18E-03	192400	660317	148989
		mistblower (hh)		n/a					
		backpack		150 L	5.11	0.02	19558	63799	14969
		MP HG		3800 L	122.37	0.75	817	1036	457
		MP HW		150 L	1.45	8.90E-03	69086	87653	38635
Greenhouse Peppers	WSP	mistblower (auto)	8.40E-03 (kg a.i./L)	5000 L	0.42	9.50E-04	240500	825397	186236
		mistblower (hh)		n/a					
		backpack		150 L	4.09	9.78E-03	24447	79748	18711
		MP HG		3800 L	97.90	0.60	1021	1295	571
		MP HW		150 L	1.16	7.12E-03	86358	109566	48294
Greenhouse Tomatoes	WSP	mistblower (auto)	1.05E-03 (kg a.i./L)	5000 L	0.52	1.18E-03	192400	660317	148989
		mistblower (hh)		n/a					
		backpack		150 L	5.11	0.01	19558	63799	14969
		MP HG		3800 L	122.37	0.75	817	1036	457
		MP HW		150 L	1.45	0.01	69086	87653	38635

Crop	Form [1]	Application Equipment [2]	Application Rates [3] (kg a.i./L) or (kg a.i./ha)	Area treated per day [4] (ha) or (L)	Daily Exposure (µg/kg/day)		Margins of Exposure		
					Dermal [5]	Inhalation [6]	Dermal [7]	Inhalation [8]	Combined [9]
Greenhouse Ornamentals	WSP	mistblower (auto)	1.43E-03 (kg a.i./L)	5000 L	0.71	1.61E-03	141273	484848	109367
		mistblower (hh)		n/a					
		backpack		150 L	6.96	0.02	14361	46845	10991
		MP HG		3800 L	166.66	1.03	600	760	335
		MP HW		150 L	1.97	4.52	50728	64360	28368

[1,2] WSP = Wettable Powder in Water Soluble Packaging; MP HG = mechanically-pressurized hand held spray gun; MP HW = manually-pressurized hand held spray wand; hh = hand held.
[3] Maximum listed label rate in kilograms of active ingredient per litre (kg a.i./L) using the minimum recommended spray volume.
[4] Based on standard assumptions derived from survey data.
[5] Where dermal exposure µg/kg/day = unit exposure x area treated x rate)/80 kg bw.
[6] Where inhalation exposure µg/kg/day = (unit exposure x area treated x rate)/80 kg bw, includes a 90% protection factor for respirators.
[7] Based on a dermal NOAEL of 100 mg/kg bw/day and a target dermal MOE of 300.
[8] Based on an inhalation NOAEL of 0.78 mg/kg bw/day and a target inhalation MOE of 300.
[9] Combined MOE = 1 ÷ ((1 ÷ Dermal MOE) + (1 ÷ Inhalation MOE)). Insufficient data exists to assess hand held mistblowers. Shaded cells indicate those MOEs that do not to reach the target of 300.

Table 3 Occupational Outdoor Postapplication Exposure Estimates, MOEs and REIs

Crop	Applications per Year		Rates [3] (kg a.i./ha)	Activity	Transfer Coefficient [4] (cm^2/hr)	DFR [5] ($\mu g/cm^2$)	Dermal Exposure [6] (µg/kg bw/day)	MOE [7]	REI [8] (days)
	Number [1]	Interval [2] (days)							
Apples	2	30	0.45	hand thinning	30000	0.78	234.50	426	0.5
				hand harvest	14000	0.78	109.43	914	0.5
				scouting, hand pruning, training	5800	0.78	45.34	2206	0.5
				transplanting	2300	0.78	17.98	5562	0.5
				hand weeding, propping, orchard maintenance	1000	0.78	7.82	12793	0.5
Cherries, (sweet and tart), Nectarines, Peaches	1	n/a	0.45	hand thinning	30000	0.78	234.50	426	0.5
				hand harvest	14000	0.78	109.43	914	0.5
				scouting, hand pruning, training	5800	0.78	45.34	2206	0.5
				transplanting	2300	0.78	17.98	5562	0.5
				hand weeding, propping, orchard maintenance, bird control (cherries)	1000	0.78	7.82	12793	0.5
Pears	2	30	0.54	hand thinning	30000	0.94	281.40	355	0.5
				hand harvest	14000	0.94	131.32	761	0.5
				hand line irrigation	5800	0.94	54.40	1838	0.5
				transplanting	2300	0.94	21.57	4635	0.5
				hand weeding, propping, orchard maintenance	1000	0.94	9.38	10661	0.5

[1] The maximum label listed number of applications per season.
[2] The minimum label listed application interval.
[3] Maximum listed label rates expressed in kilograms a.i./hectare.
[4] Transfer coefficients are from the 2012 PMRA Revised Agricultural Transfer Coefficients Memo (PMRA 2012).
[5] Based on DFR data, at x days after application, where x is the day when an MOE ≥ 300 is determined or the proposed REI. Orchard crops were assessed using the peak DFR and linear regression analysis from the available almond DFR study (PMRA# 2256497).
[6] Dermal exposure = DFR x TC x 8 hr ÷ 80 kg.
[7] The resulting MOE on the determined REI day. Based on the dermal NOAEL (all durations) of 100 mg/kg/day and a dermal target MOE of 300.
[8] Day at which the dermal exposure results in an MOE ≥ 300.

Table 3 Occupational Outdoor Postapplication Exposure Estimates, MOE's and REI's (continued)

Crop	Applications per Year		Rates [a] (lb a.i./Ac)	Activity	Transfer Coefficient (cm²/hr) [b]	DFR [c] (µg/cm²)	Dermal Exposure [d] (µg/kg bw/day)	MOE [e]	REI [f] (days)
	Number [1]	Interval [2] (days)							
Grapes	1	n/a	0.85	girdling, turning	10,000	0.17	327.60	3670	24
				tying/training, hand harvest, leaf pulling	8,000	0.30	516.97	2000	30
				hand set irrigation	1,750	0.78	196.88	9108	0.5
				scouting, hand weeding, bird control, propagating, netlin repair, hand pruning	6,60	0.78	72.00	13889	0.5
				transplanting	2,50	0.78	27.00	38667	0.5
Raspberries (post-harvest)	2	30	0.85	irrigation (hand set)	1,750	0.78	269.76c	5756	0.5
				tying/training (maximum foliage)	3,000	0.78	252.64	6750	0.5
				tying/training (minimum foliage), scouting, hand pruning, hand weeding	6,60	0.78	97.19	18229	0.5
				transplanting	2,50	0.78	36.83	38613	0.5
Strawberries	2	15	0.85	hand harvest	1,000	0.78	196.89	9108	0.5
				transplanting	8,000	0.78	63.10	24150	0.5
				scouting	2,00	0.78	17.60	30660	0.5
				hand weeding, canopy management	70	0.78	12.93	70970	0.5
Outdoor Ornamentals	2	28	0.82	irrigation (hand set)	1,750	0.75	259.78	5996	0.5
				all others	2,50	0.75	55.53	38613	0.5

[1] The maximum label listed number of applications per season.
[2] The minimum label listed application interval.
[3] Maximum listed label rates expressed in kilograms a.i./hectare.
[4] Transfer coefficients are from the 2012 PHED Revised Agricultural Transfer Coefficients Memo (PHED's 2010).
[5] Based on DFR data, at x days after application, where x is the day when an MOE = 300 is determined. Agricultural crops were assessed using the daily dissipation rate of 5.48% from the available almond DFR study (PMRA #: 2004057) and the standard assumption of an initial deposit of 25% of the application rate.
[6] Dermal exposure = DFR x TC x 8 hr / 80 kg.
[7] The resulting MOE on the determined REI day. Based on the dermal NOAEL (all durations) of 100 mg/kg/day and a dermal target MOE of 300.
[8] Day at which the dermal exposure results in an MOE = 300.

Table 4 Occupational Greenhouse Postapplication Exposure Estimates, MOEs and REIs

Crop	Applications per Cycle		Rates [3] (kg a.i./ha)	Activity	Transfer Coefficient (cm^2/hr) [4]	DFR [5] (µg/ cm^2)	Dermal Exposure [6] (µg/kg bw/day)	MOE [7]	REI [8] (days)
	Number [1]	Interval [2] (days)							
Greenhouse Cucumbers	2	28	0.53	all	1400	2.65	371.00	270	0.5
Greenhouse Tomatoes	2	30	0.32	all	1400	1.60	224.00	446	0.5
Greenhouse Peppers	2	30	0.42	all	1400	2.10	294.00	340	0.5
Greenhouse Ornamentals (potted)	2	28	0.63	all	230	0.98	22.57	4431	0.5
Greenhouse Cut Flowers	2	28	0.63	hand harvest, hand disbudding, hand pruning	4000	0.98	392.54	255	0.5
						0.83	333.03	300	6
				all other activities	230	0.98	22.57	4431	0.5

[1] The maximum label listed number of applications per season.
[2] The minimum label listed application interval.
[3] Maximum listed label rates expressed in kilograms a.i./hectare.
[4] Transfer coefficients are from the 2012 PMRA Revised Agricultural Transfer Coefficients Memo (PMRA, 2012).
[5] Based on DFR data, at x days after application, where x is the day when an MOE ≥ 300.
[6] Dermal exposure = DFR x TC x 8 hr ÷ 80 kg. Greenhouse ornamental crops were assessed using the peak DFR and linear regression analysis of the available greenhouse DFR study (PMRA #229445). Greenhouse vegetable crops were assessed using a 25% initial deposition and a dissipation rate of 0% based on standard assumptions.
[7] The resulting MOE on the day of the final application (0.5 days) and at the determined REI day. Based on the dermal NOAEL (all durations) of 100 mg/kg/day and a dermal target MOE of 300. Shaded cells indicate those calculated MOEs that do not meet the target MOE of 300.
[8] Day at which the dermal exposure results in an MOE ≥ 300.

Appendix X Environmental Risk Assessment

Table 1 Major Groundwater and Surface Water Model Inputs for Level 1 Estimated Environmental Concentrations

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	Fruits
	Maximum allowable application rate per year (g a.i./ha)	1080
	Maximum rate each application (g a.i./ha)	540
	Maximum number of applications per year	2
	Minimum interval between applications (days)	30
	Method of application	Ground spray or air blast
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	Stable
	Photolysis half-life in water (minutes)	6.2
	Adsorption K_d (mL/g)	197.6 (20th percentile of five values)
	Aerobic soil biotransformation half-life (days)	163 (90th percentile confidence bound on mean of 5 half-life values adjusted to 25°C)
	Aerobic aquatic biotransformation half-life (days)	38 (larger of two values)
	Anaerobic aquatic biotransformation half-life (days)	Stable (no data)

Table 2 Level 1 Estimated Environmental Concentrations of Pyridaben in Potential Drinking Water Sources

Compound	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)			
			Reservoir		Dugout	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Daily[3]	Yearly[4]
Pyridaben	0	0	4.4	0.4	Not reported	Not reported

[1] 90th percentile of daily average concentrations
[2] 90th percentile of yearly average concentrations
[3] 90th percentile of yearly peak concentrations
[4] 90th percentile of yearly average concentrations

Table 3 Fate and Behaviour in the Terrestrial and Aquatic Environment

Property	Value	Major Transformation Products	Comments	PMRA No.
Abiotic transformation				
Hydrolysis	No hydrolysis occurred over a 30-d period at pH 5, 7, 9	None	Stable	PMRA 1146006 1256235 (DER)
Phototransformation in water	DT_{50}= 6.8 min	Major: B-3 (max 13.3% AR), W-1 (max 29.7% AR) Minor: D-1, P-14, UK-1, UK-2	Phototransformation is a major route of transformation in water.	EFSA 2010
Phototransformati	DT_{50} = 15.8 d	PB-14/PB-22 and P-	Phototransformation is	PMRA 1170947

Property	Value	Major Transformation Products	Comments	PMRA No.
on in soil	DT_{50} = 10.9 d	14 = 22% of AR PB-22: 13%; unsure if declining at study termination	a route of transformation in soil.	1256335 (DER) EFSA 2010
Photochemical oxidative transformation - air	DT_{50} = 4.8 h (derived from Atkinson model)	Was determined via modelling so no TPs could be determined	Not persistent in air	EFSA 2010
Biotransformation				
Biotransformation in aerobic soil	DT50: 50-199 days	None	Moderately persistent to persistent	PMRA 1145997, 1146007 1256236 (DER) USEPA 2010 PMRA 2294500 PMRA 2294501
Biotransformation in anaerobic soil	Little transformation	None	Persistent	PMRA 1170949 1256331 (DER) EFSA 2010
Biotransformation Aerobic soil/water systems	DT_{50}: Whole system: 7-53 days Water: 0.39-7.7 days Sediment: 49.4-207 days	PB-7:	Whole system: Non-persistent to slightly persistent Water: non-persistent Sediment: moderately persistent to persistent	EFSA 2010
Biotransformation Anaerobic - Aquatic	No data – Data Waiver	-	Persistent	PMRA 1170953
Mobility				
Adsorption / desorption in soil	PYD Koc = 34,900-2,150,000 P-14 Koc = 0-54.9 PB-4 Kfoc = 1096-3944 PB-7 Kfoc = 115-5201 PB-22 Kfoc = 10-140	-	PYD: Immobile P-14: High to very high PB-4: Slight to low PB-7: Immobile to highly mobile PB-22: Immobile to highly mobile	PMRA 1145995 1256237 (DER) PMRA 1170950 1256238 (DER) EFSA 2010 " " "
Soil leaching	Approximately 15% of AR was P-14 in the eluent	-	Pyridaben did not leach P-14 was observed to leach.	
Volatilization	No data	-	-	-
Field studies				
Field dissipation/ Field leaching	DT50 Canada/Northern US = 5.5-67 days	PB-4: 17%AR declined to <LOQ at study termination	Non-persistent to moderately persistent Not expected to leach to groundwater under operational use conditions.	PMRA 1170972 PMRA 1170973 1256234 (DER)

Property	Value	Major Transformation Products	Comments	PMRA No.
	Denmark Spain	5-128 days		EFSA 2010
Outdoor Aquatic microcosms	DT50: Water: 0.04-2.94 days Sediments: 9.8 days		Non-persistent in water and sediment	PMRA 1170993 1256323, 1256334 (DER) PMRA 1170994 1256231 (DER) PMRA 1170995
Bioconcentration/bioaccumulation				
BCF rainbow trout BCF fathead minnow	Muscle: 139-166 Viscera: 1279-1481 Carcass:145-183 Whole fish: 1420-2360		Does not meet TSMP criteria	PMRA 1170985, 1256232 (DER). PMRA 1171001, USEPA 2010

Table 4 Estimated Environmental Concentrations in Soil and Water

Compartment		Estimated Environmental Concentrations	Drift (59%) EEC
Soil		0.45 mg/kg	-
Water	80 cm	107 µg/L	63.1 µg/L
	15 cm	568 µg/L	335 µg/L
Runoff	80 cm	Peak: 6.2 µg/L 21d: 3.0 µg/L	-
	15 cm	Peak: 12 µg/L 21d: 1.6 µg/L	-

Application of pyridaben; 2 X 540 g a.i./ha.

Table 5 Level 1 Aquatic Ecoscenario Modeling Estimated Environmental Concentrations (µg a.i./L) for Pyridaben in a Water Body 0.8 m Deep, Excluding Spray Drift

Region	Estimated Environmental Concentrations (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Berry use, 2 x 450 g a.i./ha, at 30-day intervals						
ON/QC	3.6	1.7	1.3	1.1	0.88	0.34
Prairie	5.8	1.6	0.93	0.65	0.64	0.23
Atlantic	6.2	4.2	3.0	2.4	2.3	0.72
BC	1.7	0.64	0.37	0.17	0.12	0.031
Tree use, 2 x 540 g a.i./ha, at 30-day intervals						
BC	0.15	0.034	0.0093	0.0039	0.0026	0.00089
Atlantic	1.7	0.8	0.55	0.36	0.28	0.078
ON/QC	1.8	0.41	0.26	0.17	0.12	0.047

Table 6 Level 1 Aquatic Ecoscenario Modelling EECs (µg a.i./L) for Pyridaben in a Water Body 0.15 m Deep, Excluding Spray Drift.

Region	Estimated Environmental Concentrations (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Berry use, 2 x 450 g a.i./ha, at 30-day intervals						
ON/QC	12*	2.5	0.66	0.53	0.43	0.19
Prairie	12*	4.4	1.1	0.53	0.39	0.12
Atlantic	12*	5.2	1.6	1.1	1.0	0.39
BC	9.5	1.2	0.33	0.17	0.12	0.038
Tree use, 2 x 540 g a.i./ha, at 30-day intervals						
BC	0.86	0.11	0.021	0.007	0.005	0.0012
Atlantic	9.6	1.3	0.32	0.15	0.11	0.047
ON/QC	10	1.3	0.27	0.12	0.085	0.032

Values above the solubility (marked with *) are reported as the solubility (12 µg a.i./L)

Table 7- Selected Toxicity Endpoints Used for Environmental Risk Assessment

Organism	Exposure	Test Substance	Toxicity Endpoint	Uncertainty Factor	Adjusted Toxicity Factor for Risk Assessment
Terrestrial Biota					
Earthworm	14 d- Acute	TGAI	LC_{50} = 38 mg a.i./kg	2	19 mg a.i./kg soil
Honey bee	44-h Contact Acute Oral Tunnel Test	TGAI TGAI EUP	LD_{50} 0.024 µg a.i./bee LD_{50}: 0.535 µg a.i./bee NOEC <0.15 kg a.i./ha	1	LD_{50} 0.024 µg a.i./bee LD_{50}: 0.535 µg a.i./bee NOEC <0.15 kg a.i./ha
Beneficial arthropods	Lethal Residues	EUP	LR_{50} 0.24 g a.i./ha	1	LR_{50} 0.24 g a.i./ha
Birds Bobwhite quail/Mallard duck	Acute Oral	TGAI	LD_{50}: > 2,250 mg a.i./kg bw	10	225 mg a.i./kg bw
	Reproduction	TGAI	NOEC/LOEC: 100/500 mg a.i./kg diet	1	NOEL = 5.81 mg a.i./kg bw/day
Mammals	Acute	TGAI	LD_{50}: 161 mg a.i./kg bw	10	16.1 mg a.i./kg bw
	Reproductive	TGAI	5 mg a.i./kg bw/day	1	5 mg a.i./kg bw/day
Terrestrial Plants	Tier 1 Vegetative Vigour	TGAI	EC_{25} >0.56 kg a.i./ha	1	0.56 kg a.i./ha
	Tier 1 Seed Germination/Seedling Emergence	TGAI	EC_{25}: >0.56 kg a.i./ha EC_{25} onion, ryegrass, oat, soybean, lettuce, radish, cucumber, cabbage: >0.56 kg a.i./ha	1	0.56 kg a.i./ha
Aquatic Biota					
Freshwater Invertebrates	48-h acute	TGAI	EC_{50}: 0.53 µg a.i./L	2	0.265 µg a.i./L
	life-cycle	TGAI	NOAEC = 0.044 µg a.i./L	1	0.044 µg a.i./L
Freshwater Fish	96- acute	TGAI	LC_{50} = 0.73 µg a.i./L	10	0.073 µg a.i./L
	301-d life cycle	TGAI	NOEC: 0.277µg a.i./L	1	0.28 µg a.i./L
Amphibians Based on Freshwater fish acute EC_{50} and life cycle study	96- acute	TGAI	LC_{50} = 0.73 µg a.i./L	10	0.073 µg a.i./L
	301-d full life cycle	TGAI	NOEC/LOEC: 0.277/0.555 µg a.i./L	1	0.28 µg a.i./L

Organism	Exposure	Test Substance	Toxicity Endpoint	Uncertainty Factor	Adjusted Toxicity Factor for Risk Assessment
Freshwater Algae (*Anabaena*)	5-day Acute	TGAI	EC_{50}: >13.4 µg a.i./L	2	6.7 µg a.i./L
Freshwater Vascular plant (*Lemna*)	14-d	TGAI	EC_{50}: >16.2 µg a.i./L	2	8.1 µg a.i./L
Saltwater Invertebrate (*Mysid*)	96-h acute	TGAI	LC_{50}: 0.67 µg a.i./L	2	0.335 µg a.i./L
	35-d chronic	TGAI	NOEC: 0.047 µg a.i./L	1	0.047 µg a.i./L
Saltwater Fish Sheepshead Minnow	96-h acute	TGAI	LC_{50}: 17.2 µg a.i./L	10	1.72 µg a.i./L
	Chronic	No information Data Gap			
Saltwater Diatom (*Skeletonema*)	Acute	TGAI	>16.1 µg a.i./L	2	8.1µg a.i./L

Table 8 Exceedance of Level of Concern in Terrestrial Invertebrates and Plants

Organism	RQ	Level of Concern Exceeded?	Comments
Earthworm	0.02	No	Not at risk
Honey Bee Acute Contact Acute Oral Brood	 54 29	 Yes Yes Yes	 At Risk At Risk NOEC <0.15 kg a. i./ha is much lower than any single Canadian registered application rate: 213 – 540 g a.i./ha
Beneficial Arthropods	2250	Yes	LR_{50}: 0.24 g a.i./ha is much lower than any single Canadian registered application rate: 213 – 540 g a.i./ha
Terrestrial Plants	0.96 1.81	No Yes	Not at risk after a single application at the maximum rate At Risk after maximum cumulative application rate

Table 9 Screening Level Risk Quotients for Avian Species Using Maximum Application Rate of Two Applications of 540 g a.i./ha 30 Days Apart (as Used on Pears) and Maximum Nonogram Residues and Refined EDEs Risk Assessment Using Mean Nomogram Food Residue Values

		Screening Level Risk Assessment					Refined Risk Assessment			
	Toxicity[1] (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE[3] (mg a.i./kg bw)	On-Field RQ[2]	Off-field EDE (mg a.i./kg bw)	Off-Field RQ	On-Field EDE (mg a.i./kg bw)	On-Field RQ	Off-Field EDE (mg a.i./kg bw)	Off-Field RQ
Small Bird (0.02 kg)										
Acute	225.00	Insectivore (small insects)	30.61	0.14	18.06	0.08	-	-	-	-
Reproduction	5.81	Insectivore (small insects)	30.61	**5.27**	18.06	**3.11**	17.07	**2.94**	10.07	**1.73**
Medium Sized Bird (0.1 kg)										
Acute	225.00	Insectivore (small insects)	23.89	0.11	14.09	0.06	-	-	-	-
Reproduction	5.81	Insectivore (small insects)	23.89	**4.11**	14.09	**2.43**	13.32	**2.29**	7.86	**1.35**
Large Sized Bird (1 kg)										
Acute	225.00	Herbivore (short grass)	24.93	0.11	14.71	0.07	-	-	-	-
Reproduction	5.81	Herbivore (short grass)	24.93	**4.29**	17.71	**2.53**	8.85	**1.52**	5.22	0.90

[1] Endpoints were divided by an uncertainty factor to account for varying protection goals (protection at the community, population, or individual level).

[2] RQ = exposure/toxicity; RQs < 0.1 were not calculated to show all decimal points. RQs are based on estimated environmental concentrations (EEC). For birds and mammals, the EEC takes into account the maximum seasonal cumulative rate on vegetation and is calculated using PMRA standard methods based on the Hoerger and Kenaga nomogram as modified by Fletcher (1994).

[3] EDE = Estimated dietary exposure, calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) x EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:

Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = $0.398(BW\text{ in g})^{0.850}$

All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(BW\text{ in g})^{0.651}$

All Mammals Equation: FIR (g dry weight/day) = $0.235(BW\text{ in g})^{0.822}$

Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet) x BW (g) x FIR (g of diet)] Nagy, K. A. 1987. Field metabolic rate and food requirement scaling in mammals and birds. Ecological Monographs 57:111-128

Table 10 Screening Level Risk Questients for Mammals (Maximum Application Rate of 560 g a.i./L Applied Twice with a 30-Day Interval on Pears) – On-Field

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	On-Field EEC (mg a.i./kg bw)	On-Field RQ
Small Mammal (0.015 kg)				
Acute	LC50	Insectivore (small insects)	17.61	1.09
Reproduction	NOEL	Insectivore (small insects)	17.61	2.52
Medium-Sized Mammal (0.035 kg)				
Acute	LC50	Herbivore (short grass)	55.16	3.63
Reproduction	NOEL	Herbivore (short grass)	55.16	11.63
Large-Sized Mammal (1 kg)				
Acute	LC50	Herbivore (short grass)	29.49	1.02
Reproduction	NOEL	Herbivore (short grass)	29.49	2.30

Table 11 Screening Level Risk Questients for Mammals (Maximum Application Rate of 560 g a.i./L Applied Twice with a 30-Day Interval on Pears) – Off-Field

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	Off-Field EEC (mg a.i./kg bw)	Off-Field RQ
Small Mammal (0.015 kg)				
Acute	LC50	Insectivore (small insects)	10.59	0.67
Reproduction	NOEL	Insectivore (small insects)	10.59	1.51
Medium-Sized Mammal (0.035 kg)				
Acute	LC50	Herbivore (short grass)	33.20	2.18
Reproduction	NOEL	Herbivore (short grass)	33.20	6.98
Large-Sized Mammal (1 kg)				
Acute	LC50	Herbivore (short grass)	17.75	1.09
Reproduction	NOEL	Herbivore (short grass)	17.75	3.45

Table 12 Refined Risk Questients for Mammals Using Mean Nonagrous Residue Values (Maximum Application Rate of 560 g a.i./L Applied Twice with a 30-Day Interval on Pears)

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	On-Field RQ	Off-Field RQ
Small Mammal (0.015 kg)				
Acute	LC50	Insectivore (small insects)	0.42	0.26
Reproduction	NOEL	Insectivore (small insects)	0.96	0.58
Medium-Sized Mammal (0.035 kg)				
Acute	LC50	Herbivore (short grass)	1.39	0.91
Reproduction	NOEL	Herbivore (short grass)	2.92	1.76
Large-Sized Mammal (1 kg)				
Acute	LC50	Herbivore (short grass)	0.67	0.41
Reproduction	NOEL	Herbivore (short grass)	1.40	0.84

Table A-2 Screening-Level Risk Questions for Aquatic Biota (Maximum Application Rate of 340 g a.i./A, Applied Twice with a 30-Day Interval On Pears)

Organism	Exposure Type	Endpoint value (µg a.i./L)	EEC (µg/L)	RQ
Freshwater Species				
Daphnia magna	Acute	0.269	107	400
	Chronic	0.0388	107	2800
Amphibian	Acute	0.877	308	351
	Chronic	0.36	308	860
Rainbow trout	Acute	0.877	107	0.800
	Chronic	0.36	107	300
Freshwater algae	Acute	0.7	107	>100
Freshwater Vascular plant	Acute	8.8	107	>12
Marine Species				
Crustacean	Acute	0.109	107	980
	Chronic	0.0387	107	2800
Sheepshead Minnow	Acute	1.79	107	60
Saltwater Diatom	Acute	8.8	107	>12

1/ Indicates that the RQ is an overestimate because the endpoint was > value

Table A-3 Refined Risk Assessment for Aquatic Biota Using 1-in-10-Year Drift Concentration and 10-Minute Runoff Estimated Environmental Concentrations from Conservative Water Modeling

Organism	Exposure Type	Adjusted Endpoint Value (µg a.i./L)	Spray Drift (90th%) EEC (µg a.i./L)	Spray Drift RQ	Acute or Chronic Maximum Runoff EEC's	Acute or Chronic Runoff RQ
Freshwater Species						
Daphnia magna	Acute	0.269	60.80	226	0.2	30
	Chronic	0.0388	60.80	1600	2	40
Amphibian	Acute	0.877	308.8	4000	10	100
	Chronic	0.36	308.8	1000	0.6	6
Freshwater Fish	Acute	0.877	60.80	69.2	0.2	40
	Chronic	0.36	60.80	200	2	10
Freshwater algae	Acute	0.7	60.80	>86.9	0.2	>0.3 [1]
Freshwater Vascular plant	Acute	8.8	60.80	>6.9	0.2	>0.8 [1]
Marine species						
Crustacean	Acute	0.109	60.80	560	0.2	10
	Chronic	0.0387	60.80	1600	2	40
Sheepshead Minnow	Acute	1.79	60.80	37	0.2	0
Marine Diatom	Acute	8.8	60.80	>6.9	0.2	>0.8 [1]

1/ Indicates that the RQ is an overestimate because the endpoint was > value

Table 15 Refined Risk Quotients for Aquatic Biota Using Runoff Estimated Environmental Concentrations Determined for Each Canadian Region Using Ecoscenario Water Modelling Water Concentrations

Regional EEC (µg a.i./L)		Daphnia RQ	Amphibian RQ	FW Fish RQ	FW algae RQ	FW Vascular plant RQ	Marine Invertebrate RQ	Marine Fish RQ	Marine Diatom RQ
Acute Toxicity									
Toxicity Endpoints µg a.i./L		0.265	0.073	0.073	6.7	8.1	0.135	1.72	8.1
96-h EEC Berry Use 2 x 450 g a.i./ha									
ON/QC	1.7	6.4	23.3	23.3	0.3	0.2	5.1	1.0	0.1
Prairie	1.6	6.0	21.9	21.9	0.2	0.2	4.8	0.9	0.1
Atlantic	4.2	15.8	57.5	57.5	0.6	0.5	12.5	2.4	0.3
BC	0.64	2.4	8.8	8.8	0.1	0.1	1.9	0.4	0.0
96-h EEC Tree Use 2 x 560 g a.i./ha									
ON/QC	0.034	0.1	0.5	0.5	0.0	0.0	0.1	0.0	0.0
Atlantic	0.8	3.0	11.0	11.0	0.1	0.0	2.4	0.5	0.1
BC	0.41	1.5	5.6	5.6	0.1	0.1	1.2	0.2	0.0
Chronic Toxicity									
Toxicity Endpoints µg a.i./L		0.044	0.28	0.28	ND	ND	0.047	2.1	ND
21-d EEC Berry Use 2 x 450 g a.i./ha									
ON/QC	1.1	25.5	4.6	4.6	-	-	27.7	0.6	-
Prairie	0.93	21.1	3.3	3.3	-	-	19.8	0.4	-
Atlantic	3	68.2	10.7	10.7	-	-	63.8	1.4	-
BC	0.37	8.4	1.3	1.3	-	-	7.9	0.2	-
21-d EEC Tree Use 2 x 560 g a.i./ha									
ON/QC	0.0093	0.2	0.0	0.0	-	-	0.2	0.0	-
Atlantic	0.55	12.5	2.0	2.0	-	-	11.7	0.3	-
BC	0.26	5.9	0.9	0.9	-	-	5.5	0.1	-

ND = No Data

Table 16 Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion Value		Active Ingredient Endpoints	Transformation Products Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act* [1]	Yes		**Meets Criteria**	**PB-7 Meets Criteria** **PB-22 Does Not Meet**
Predominantly anthropogenic[2]	Yes		**Meets Criteria**	**Meets Criteria**
Persistence[3]	Soil	Half-life ≥ 182 days	Half-life: 50-183 days **Does Not Meet**	No Specific Information
	Water	Half-life ≥ 182 days	Half-life: 1-4 days **Does Not Meet**	No Specific Information
	Sediment	Half-life ≥ 365 days	Half-life: 51- 163 days **Does Not Meet**	No Specific Information
	Air	Half-life ≥ 2 days or evidence of long range transport	DT_{50} in air estimated to be 4.8 h **Does Not Meet**	No Specific Information
Bioaccumulation[4]	Log K_{OW} ≥ 5		6.37 **Meets Criteria**	PB-7: 3.2 PB-9: 2.6 **Does Not Meet**
	BCF ≥ 5000		**Does Not Meet**	No Information
	BAF ≥ 5000		No Information	No Information
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (in other words, all other TSMP criteria are met). [2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (such as BAFs) are preferred over laboratory data (such as BCFs) which, in turn, are preferred over chemical properties (such as log K_{OW}).

Appendix XI Water Monitoring Data

In addition to water modelling, a search for water monitoring data on pyridaben in Canada was undertaken. The PMRA regularly communicates with the Federal, Provincial and Territorial representatives from all of the provinces and territories in Canada along with Environment Canada, the Department of Fisheries and Oceans and the drinking water subcommittee through Health Canada to acquire monitoring data that would be relevant to current re-evaluation programs.

Pyridaben was part of the analyte list in two studies conducted in Alberta from 1995 to 2003. One study surveyed pesticide residues in treated water. Pyridaben was not detected in any of the 1004 samples analyzed. A second study monitored the presence of pesticides in surface waters from 1995 to 2002. Pyridaben was detected once out of 2481 samples at 0.03 µg/L. The limit of detection was 0.02 µg/L in both studies. This dataset consisted of an aggregation of pesticide data collected from all surface water quality projects managed by Alberta Environment and included a broad range of water bodies across the major river basins, including rivers, creeks, lakes, wetlands, irrigation canals, irrigation return flows, and urban streams and drains.

The United States databases were also searched for monitoring of pyridaben in water. Data on residues present in water samples taken in the United States are important to consider in the Canadian water assessment given the extensive monitoring programs that exist in the United States. Local weather patterns, runoff events, circumstantial hydrogeology as well as testing and reporting methods are probably more important influences on residue data than Northern versus Southern climate. As for climate, if temperatures are cooler, residues may break down more slowly, on the other hand if temperatures are warmer, growing seasons may be longer and pesticide inputs may be more numerous and frequent.

In the United States, pyridaben was not included in the analyte list for monitoring information stored in the United States Environmental Protection Agency (USEPA) Storage and Retrieval data Warehouse, the United States Department of Agriculture Pesticide Data Program, the National Stream Quality Accounting Network, or the California Department of Pesticide Regulation. The American Geological Survey National Water Quality Assessment Program database reported a single surface water sample in the Rio Grande River in Texas in December 2013 for which pyridaben was analyzed, however, it was not detected above the limit of detection of 0.003 µg/L.

Appendix XII Proposed Label Amendments for Products Containing Pyridaben

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements below.

For Technical Grade Products:

The signal word "WARNING" and the accompanying hazard symbol (square set on point) are proposed to appear on the primary panel.

The following statements are proposed to be added in a section entitled **ENVIRONMENTAL PRECAUTIONS**:

> "TOXIC to aquatic organisms."
>
> "**DO NOT** discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters."

The following statement is proposed to be added under **DISPOSAL**:

> "Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and for clean-up of spills, contact the manufacturer or the provincial regulatory agency.

For Commercial Class Products:

The use on GRAPES is proposed to be removed from labels.

The following statements are proposed to be added under **PRECAUTIONS**:

> "Do not use in residential areas. Residential areas are defined as sites where bystanders including children may be potentially exposed during or after spraying. This includes around homes, school, parks, playgrounds, playing fields, public buildings or any other areas where the general public including children could be exposed."
>
> "Apply only when the potential for drift to areas of human habitation or areas of human activity (houses, cottages, schools and recreational areas) is minimal. Take into consideration wind speed, wind direction, temperature inversion, application equipment and sprayer settings."
>
> "Hazardous to humans and domestic animals. Keep out of reach of children and pets."
>
> "Not for use by homeowners or other uncertified users."

Changes to restricted-entry intervals (REIs) are proposed for greenhouse cut flowers (hand harvesting, hand pruning, disbudding). The following REIs are proposed to be added to the appropriate labels.

Table 1 Restricted-entry intervals

Crop	REI
Apples	1 day
cherries, nectarines, peaches	1 day
greenhouse vegetables	12 hours
greenhouse potted ornamentals	12 hours
greenhouse cut flowers – hand harvesting, hand pruning, disbudding	6 days
greenhouse cut flowers – all other tasks	12 hours
Pears	1 day
strawberries, raspberries	1 day
outdoor ornamentals	12 hours

For GREENHOUSE uses, the following statements are proposed to be added under **PRECAUTIONS:**

> "Wear waterproof rain gear, rubber boots, socks, goggles, gloves (rubber, PVC, neoprene or nitrile), hat and a NIOSH-approved dust/mist filtering respirator during mixing, loading and application."
>
> "**DO NOT** enter treated areas within 12 hours. If required, individuals may enter treated areas within 12 hours for short-term tasks not involving hand labour if at least 4 hours has passed since application and waterproof rain gear, rubber boots, socks, goggles, gloves (rubber, PVC, neoprene or nitrile), hat and a NIOSH-approved dust/mist filtering respirator are worn. Time spent in the treated area cannot exceed 1 hour in a 12-hour period."

For OUTDOOR uses, the following statements are proposed to be added under **PRECAUTIONS:**

> "Wear long-sleeved shirt, long pants, rubber boots, socks, goggles, gloves (rubber, PVC, neoprene or nitrile), hat and a NIOSH-approved dust/mist filtering respirator during mixing, loading and application."
>
> "**DO NOT** enter treated areas within 24 hours. If required, individuals may enter treated areas within 24 hours for short-term tasks not involving hand labour if at least 4 hours has passed since application and a long-sleeved shirt, long pants, rubber boots, socks, goggles, gloves (rubber, PVC, neoprene or nitrile), hat and a NIOSH-approved dust/mist

filtering respirator are worn. Time spent in the treated area cannot exceed 1-hour in a 24-hour period."

The following statements are proposed to be added under **ENVIRONMENTAL PRECAUTIONS**:

"TOXIC to bees. Bees may be exposed through direct spray, spray drift, and residues on leaves, pollen and nectar in flowering crops and weeds. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site. Avoid applications when bees are foraging in the treatment area in ground cover containing blooming weeds. To further minimize exposure to pollinators, refer to the complete guidance "Protecting Pollinators during Pesticide Spraying – Best Management Practices" on the Health Canada website (www.healthcanada.gc.ca/pollinators). Follow crop specific directions for application timing.

"For applications on crops that are highly attractive to pollinators (apples, cherries, nectarines, peaches, pears, and outdoor ornamentals), and when using managed bees for pollination services: DO NOT apply during the crop blooming period."

"For applications to strawberries: Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to evening when most bees are not foraging."

"For Greenhouse Use: Toxic to bees and other beneficial insects. May harm bees and other beneficial insects used in greenhouse production. Avoid application when bees or other beneficial insects are foraging in the treatment area."

"TOXIC to beneficial arthropods. Minimize spray drift to reduce harmful effects on beneficial arthropods in habitats next to the application site such as hedgerows and woodland."

"TOXIC to birds."

"TOXIC to small wild mammals."

"TOXIC to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE."

"TOXIC to non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE."

The following statements are proposed to be added under **DIRECTIONS FOR USE**:

"Do not apply by hand-held mistblower."

"Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets

smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground."

"Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side."

"**DO NOT** apply by air."

"As this product is not registered for the control of pests in aquatic systems, **DO NOT** use to control aquatic pests."

"**DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

"**DO NOT** allow effluent or runoff from greenhouses or mushroom houses containing this product to enter lakes, streams, ponds or other waters".

"Use of the following spray methods or equipment **DOES NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment."

"The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats."

Table 2 Buffer zones for Protection of Freshwater, Estuarine, Marine and Terrestrial Biota

Crop	Application Method	Buffer Zone (metres) Required for the Protection for Mean Depths of:				
		Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:		Terrestrial Habitat
		<1 m	>1 m	<1 m	>1 m	
Pear	Late Airblast	65	40	35	25	1
Outdoor Ornamentals	Late Airblast	65	40	35	25	1
Apples, Raspberries	Late Airblast	65	40	35	25	1
Strawberries	Field (Medium)	120	15	10	5	1
Cherries, Peaches, Nectarines	Late Airblast	60	35	30	20	1

"For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners."

"The spray drift buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site."

"To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay."

"Avoid application when heavy rain is forecast."

"Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body."

The following statements for pollinator protection are proposed to be added under **DIRECTIONS FOR USE**:

"To protect pollinators, follow the instructions regarding bees in the Environmental Precautions section."

For apples, cherries, nectarines, peaches, pears and outdoor ornamentals:
"TOXIC to bees. DO NOT apply during the crop blooming period."

For strawberries:
"TOXIC to bees. Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to evening when most bees are not foraging. When managed bees are present for pollinator services, DO NOT apply during the crop blooming period."

For greenhouse use:
"TOXIC to bees and other beneficial insects. May harm bees and other beneficial insects used in greenhouse production. Avoid application when bees or other beneficial insects are foraging in the treatment area."

The following statement is proposed to be added under **DIRECTIONS FOR USE** for GREENHOUSE CUCUMBERS:

"Use 1000 to 2500 litres of spray solution per hectare."

The following statement is proposed to be added, under **STORAGE**:

"To prevent contamination, store this product away from food or feed."

The following statement is proposed to be added under **DISPOSAL**:

"For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in case of a spill, and for clean-up of spills."

References

A. Information Considered in the Chemistry Assessment

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E. Information Considered in the Environmental Risk Assessment

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